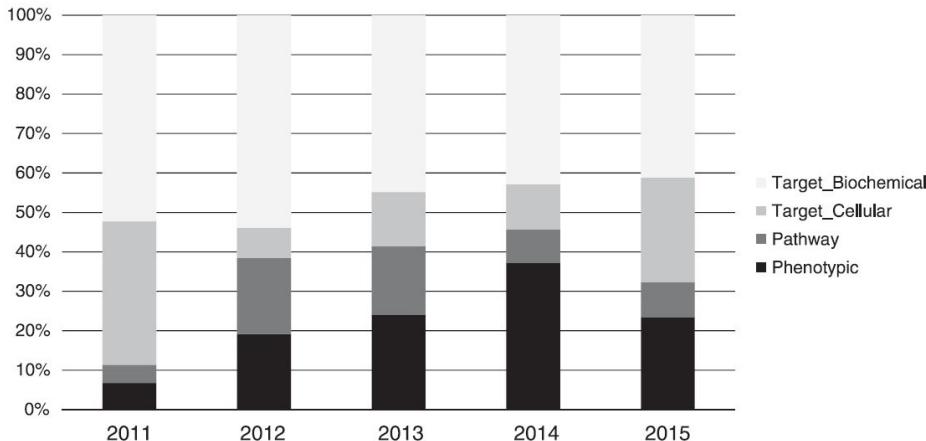
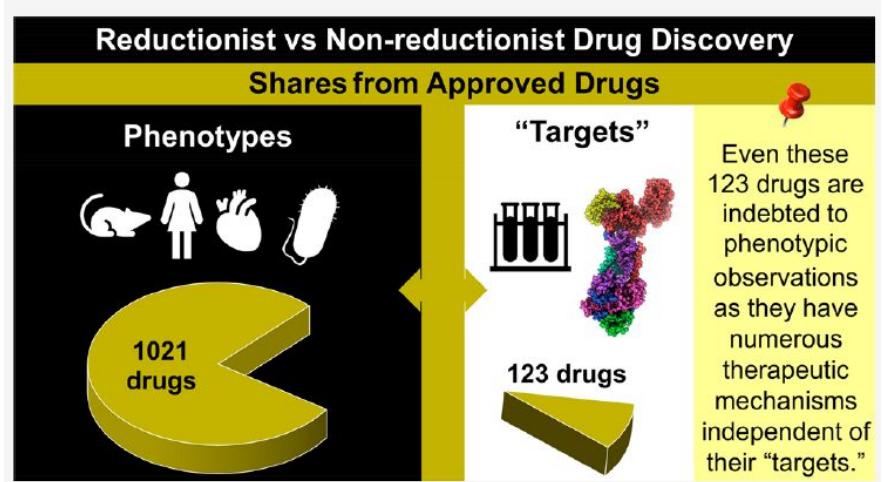


What can we do if there are no good targets

Mathematical and Computational Biology in Drug Discovery Module II

*Dr. Jitao David Zhang
March-April 2025*

Is target-based drug discovery the only way?



Sadri, Arash. 2023. "[Is Target-Based Drug Discovery Efficient? Discovery and 'Off-Target' Mechanisms of All Drugs.](#)" Journal of Medicinal Chemistry 66 (18): 12651–77.

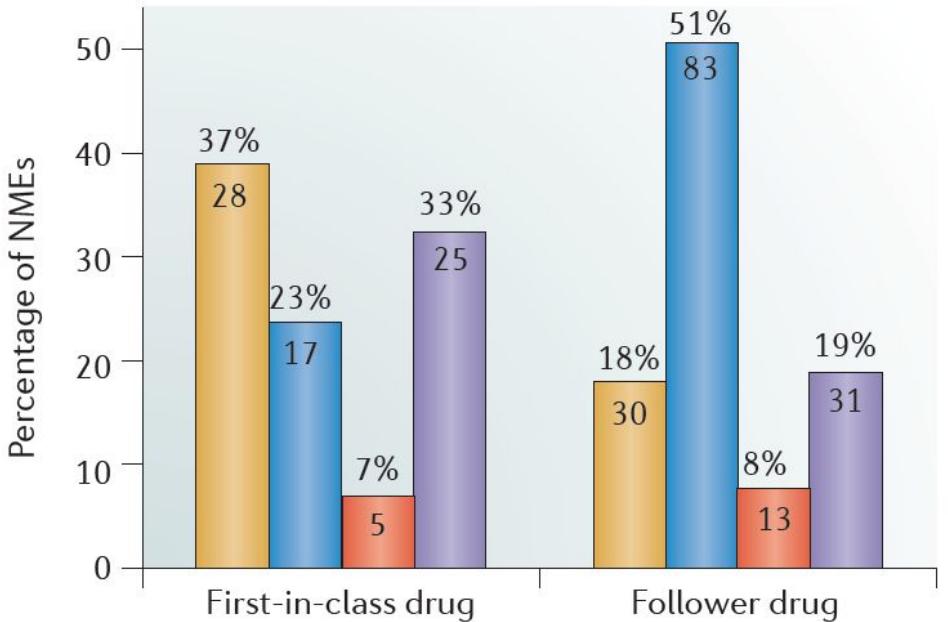
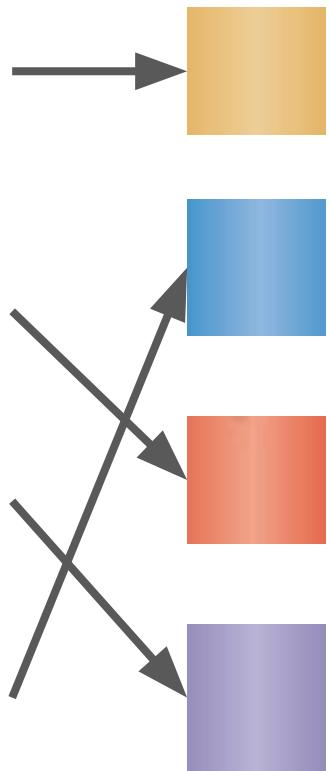
Haasen, Dorothea, Ulrich Schopfer, Christophe Antczak, Chantale Guy, Florian Fuchs, and Paul Selzer. 2017. "[How Phenotypic Screening Influenced Drug Discovery: Lessons from Five Years of Practice.](#)" ASSAY and Drug Development Technologies 15 (6): 239–46.

Five strategies when no good target is found

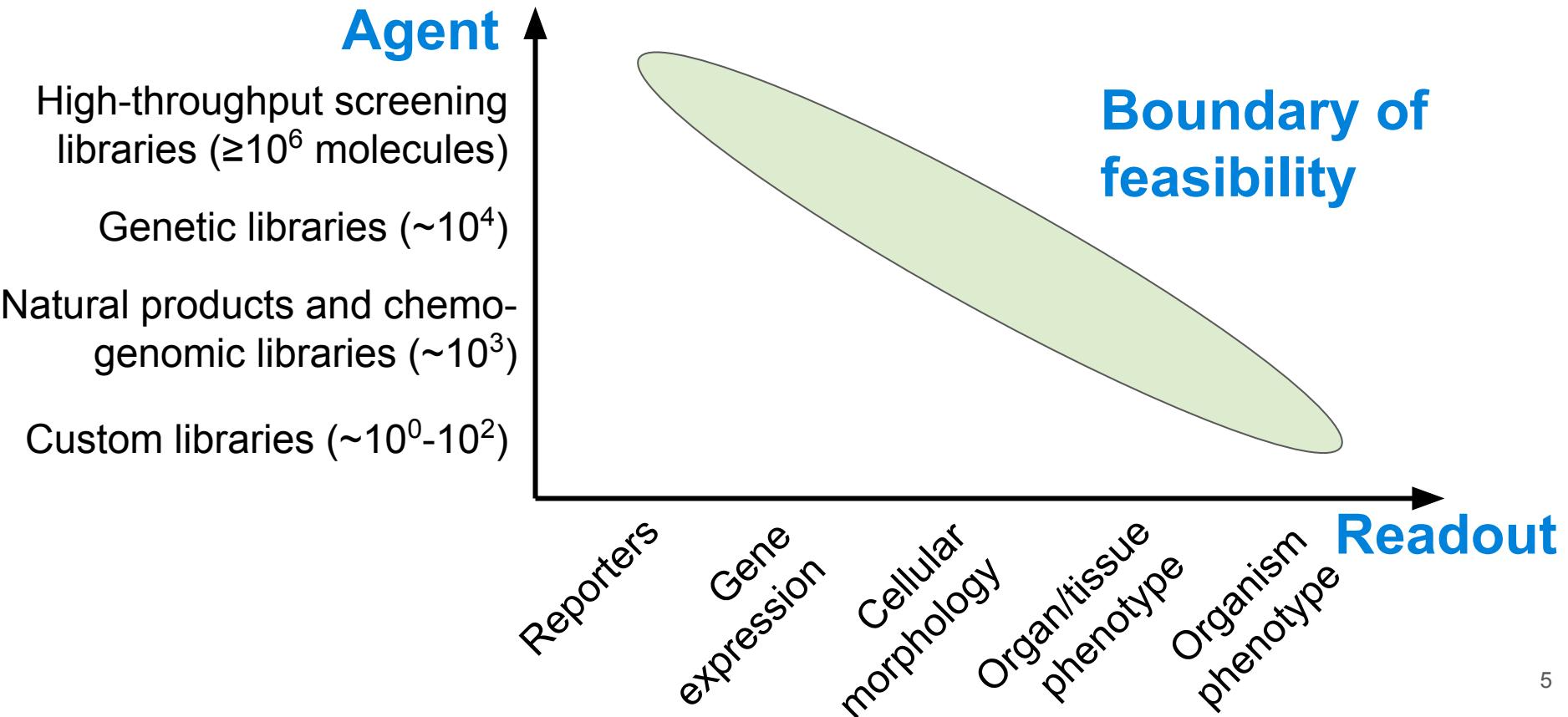
1. Phenotypic drug discovery
2. Natural products
3. Biologics
4. Interaction-based (multispecific) drug discovery
5. Drug repurposing or combination studies

Connect the lines!

- Phenotypic screening
- Modified natural products
- Biologics
- Target-based screening

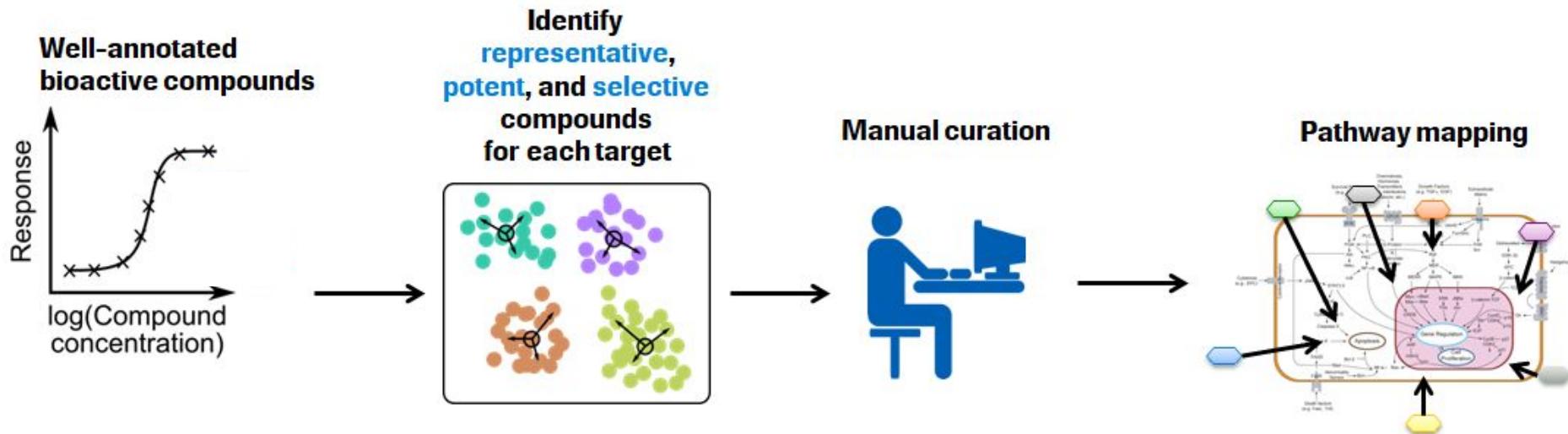


Phenotypic screenings by agent and readout



The Small-molecule PAthway Research Kit (SPARK)

Now known as the Pathway Annotated Chemical Ensemble (PACE) library



The ChEMBL database

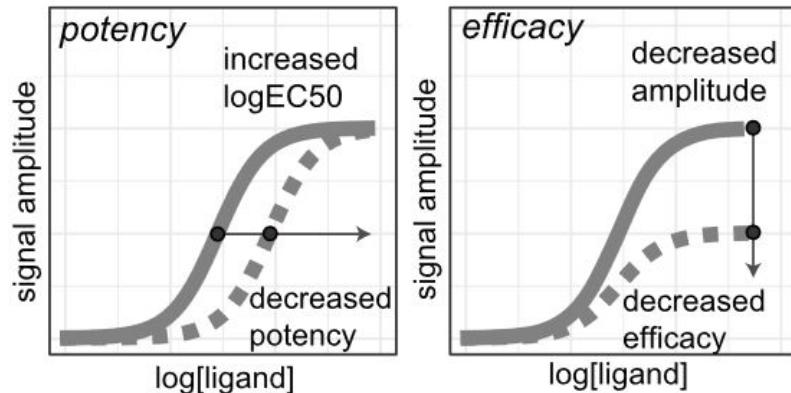
- An example of query: [aspirin](#).
- Systematic and programmatic accession via [ChEMBL API](#) ([source code](#)).
- We can use **dose-response data** to annotate the *triplets* of compound, assay activity, and targets.



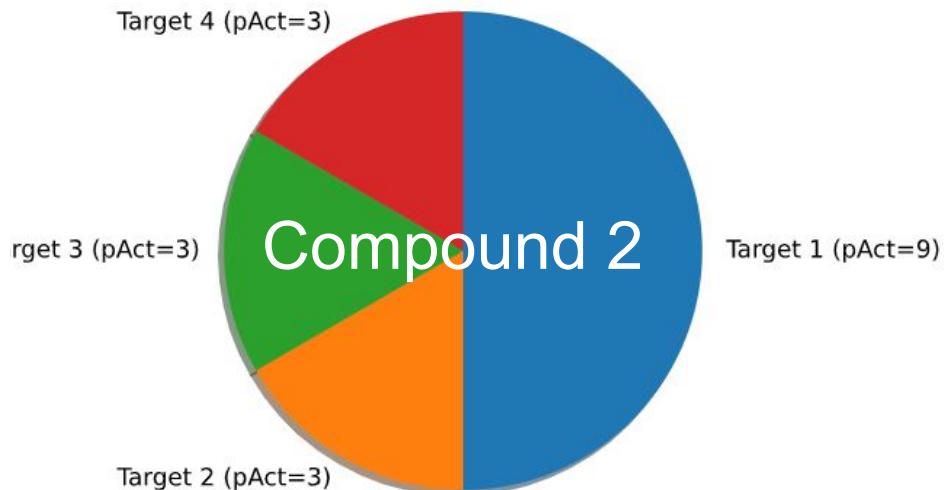
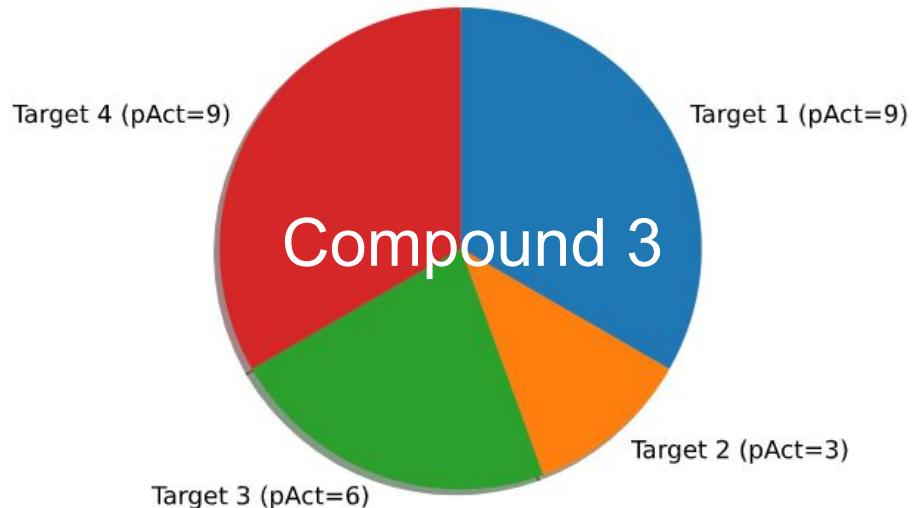
[Visualization of ChEMBL](#)
(version 33; 2024)

Discussion

1. Why do we care selecting *representative*, *potent*, and *selective* compounds?
2. How to define following terms mathematically ...
 - a. Representativity?
 - b. Potency?
 - c. Selectivity?

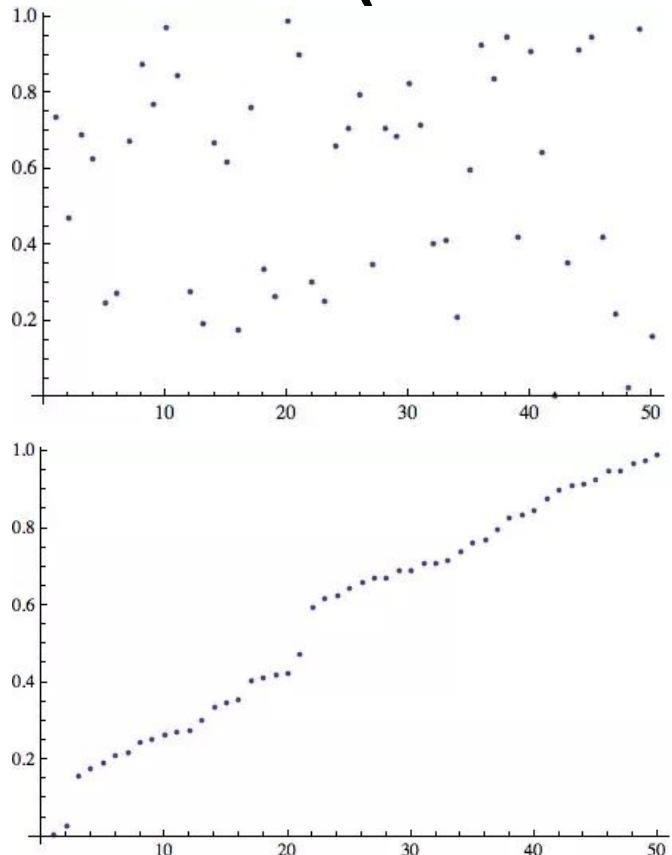


A toy example about how to quantify a compound's potency and selectivity



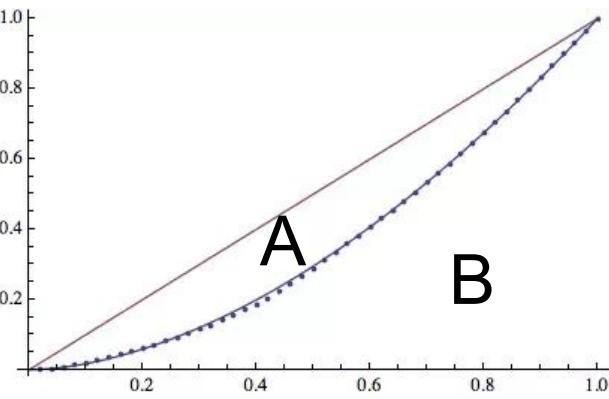
The Gini Index (a.k.a. Gini Coefficient)

A random vector of 50 values



Sorted
from low
to high

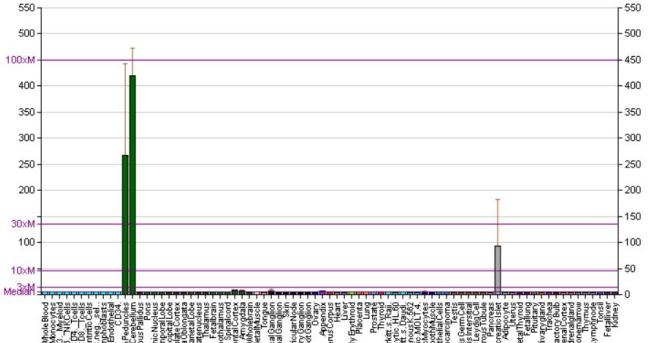
The Gini Index is calculated based on the cumulative distribution: larger value → large inequality



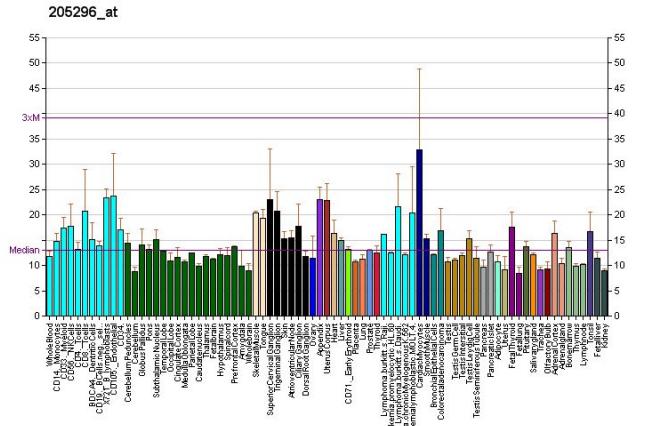
$$G = A/(A+B)$$

The Gini Index quantifies inequality/ selectivity

NEUROD1

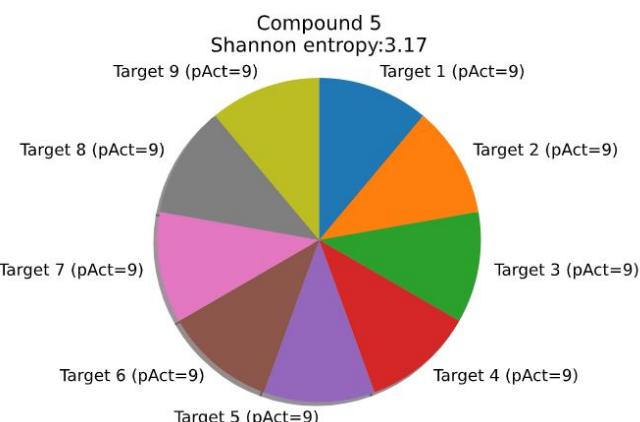
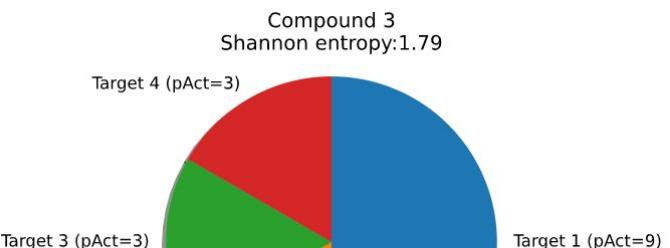
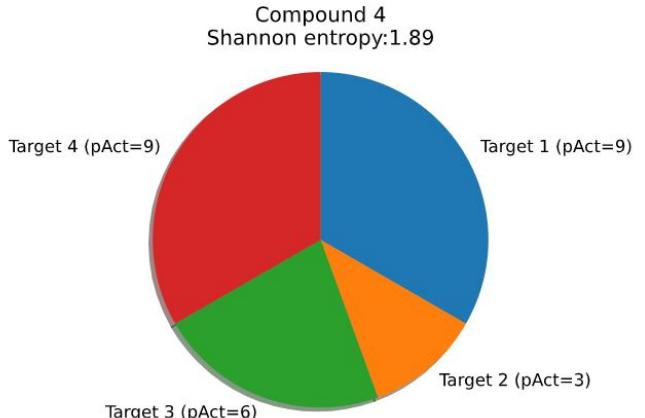
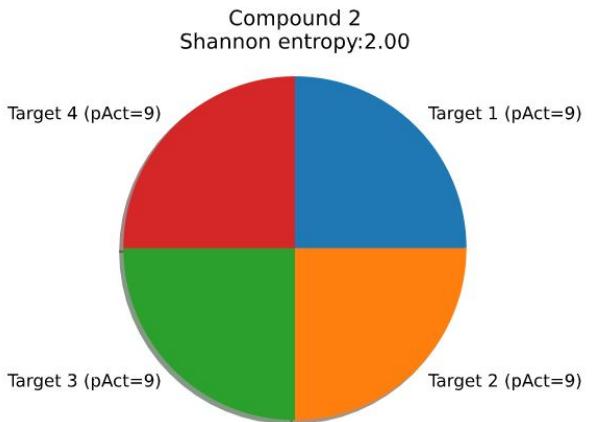
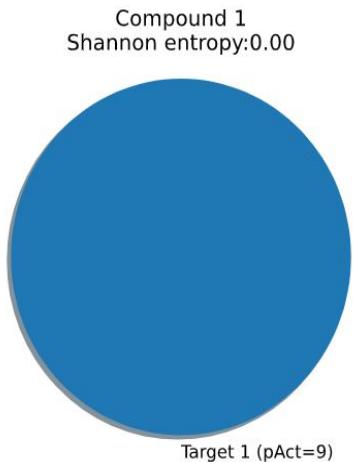


RBL1



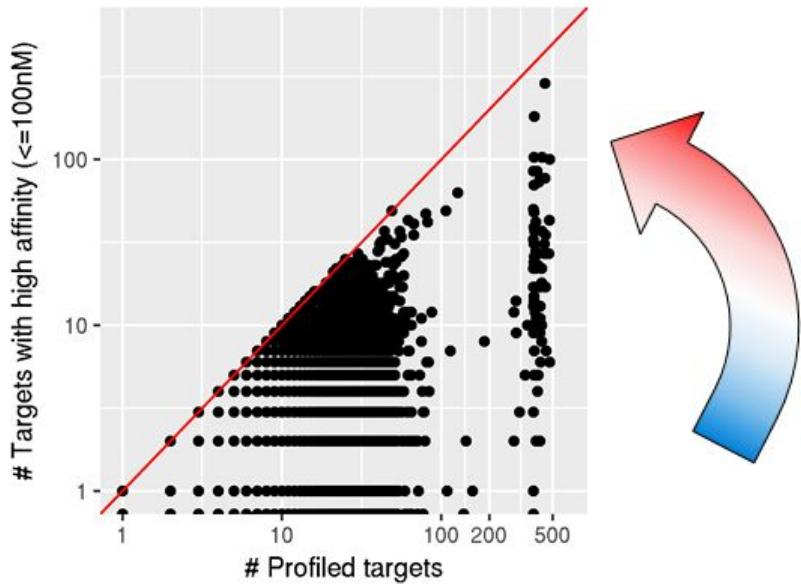
The Gini Index of expression of *NEUROD1* across tissues is near 1, whereas that of *RBL1* is near 0.

An alternative metric: Shannon's Entropy

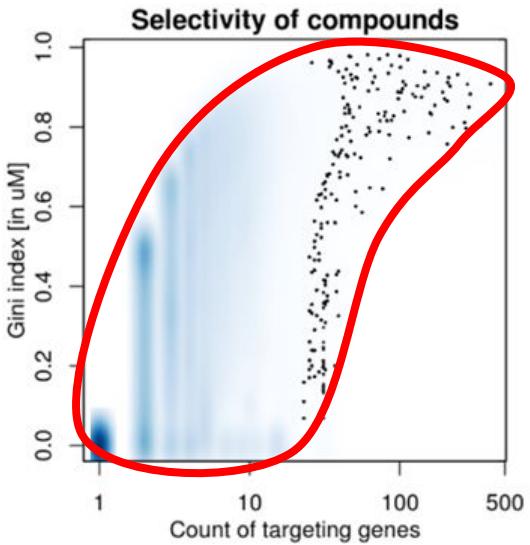


$$H(X) := - \sum_{x \in \mathcal{X}} p(x) \log p(x)$$

Count of targets and selectivity of ChEMBL molecules

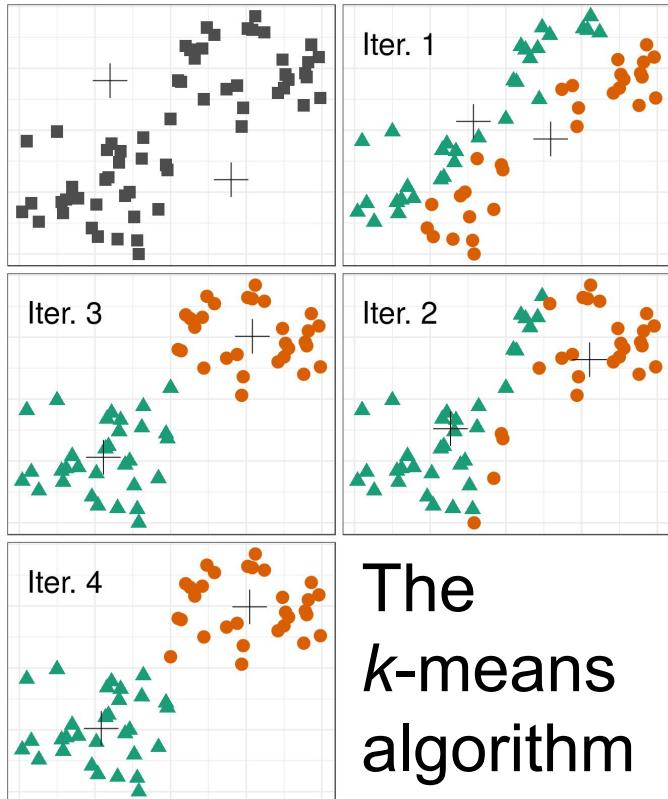


With some exceptions, most compounds are profiled against < 100 targets. We distinguish between specific and pleiotropic compounds.



The **shark-fin shape** curve suggests that frequently profiled compounds tend to be more selective (and *vice versa*).

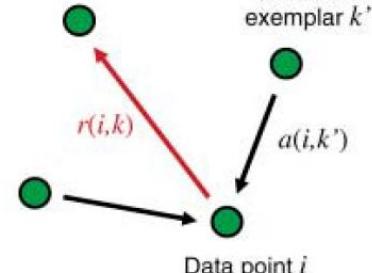
Unsupervised clustering



B

Sending responsibilities

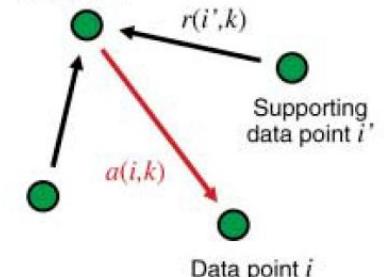
Candidate exemplar k



C

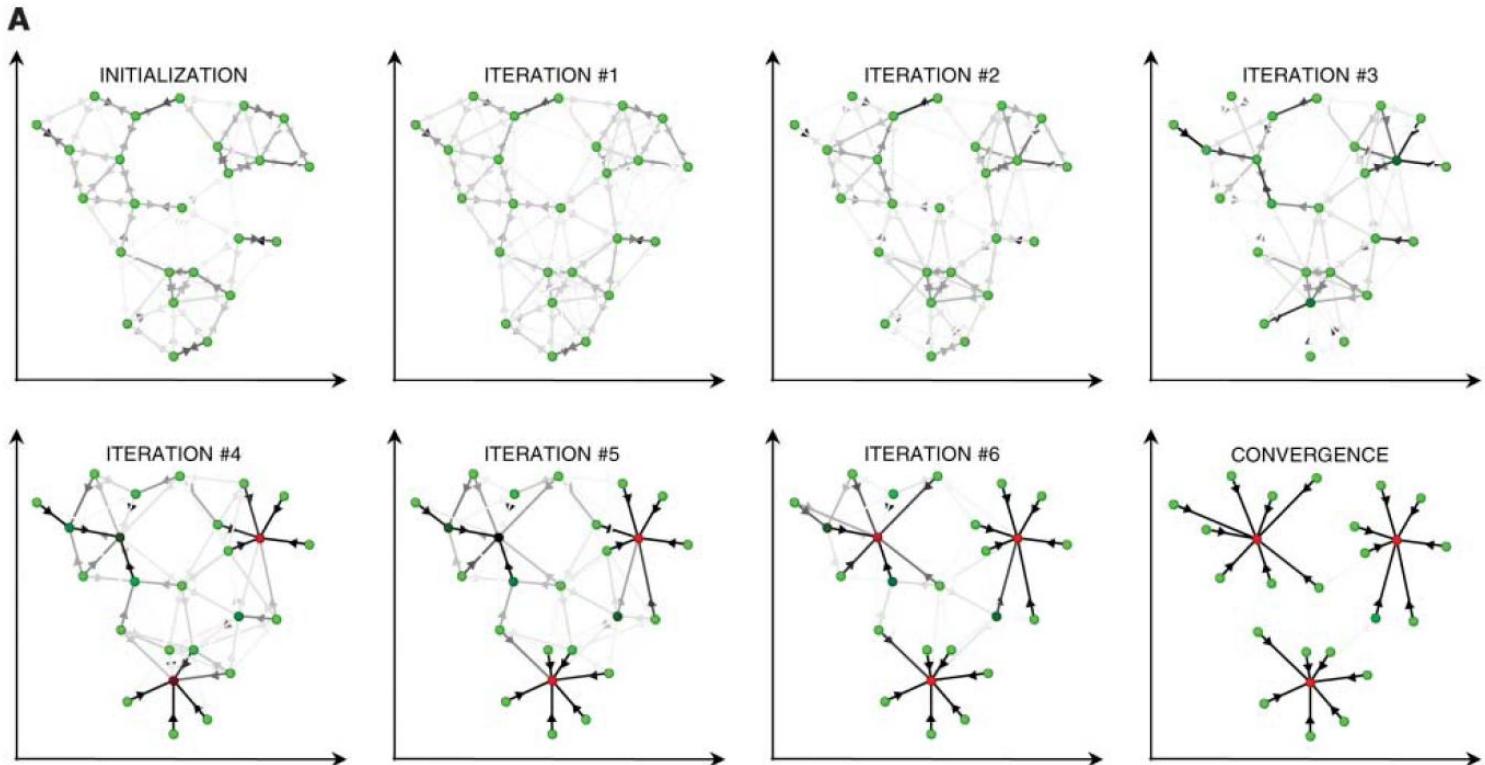
Sending availabilities

Candidate exemplar k



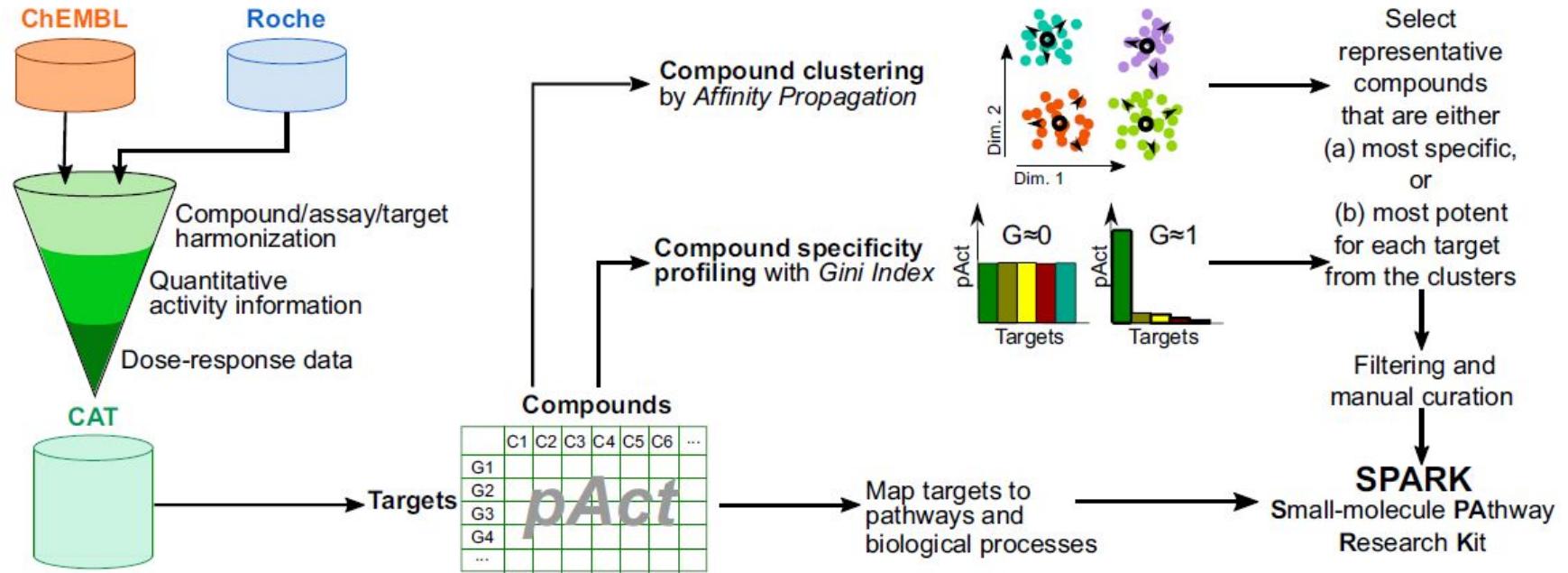
Affinity Propagation updates **responsibilities** and **availabilities** iteratively

Affinity Propagation in action



A movie of iterations

Construction of SPARK in detail



Harmonization

... of public and
Roche internal data

Machine learning

... to select
compounds

Pathways

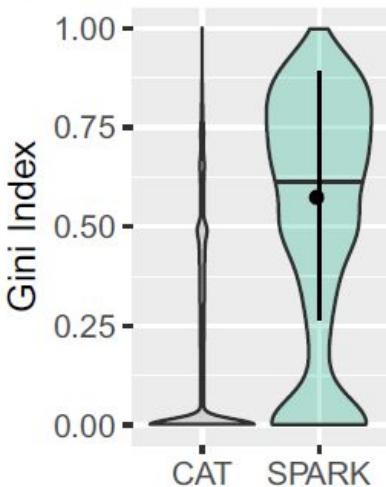
... mapped to
compounds

Curation

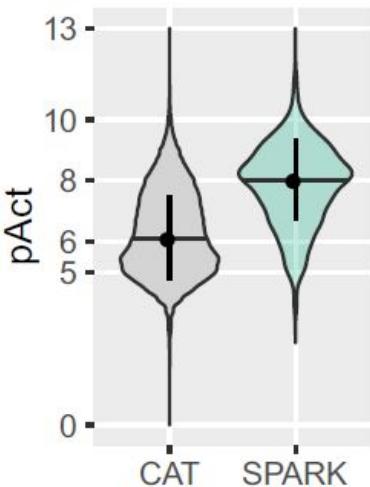
... to enrich quality
compounds

SPARK covers the chemical space evenly with representative, potent, and specific compounds

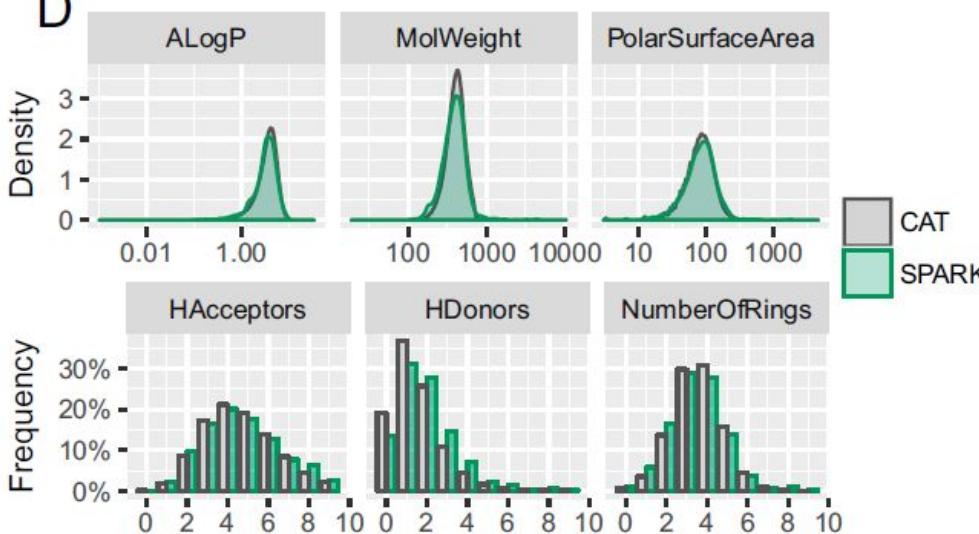
B



C

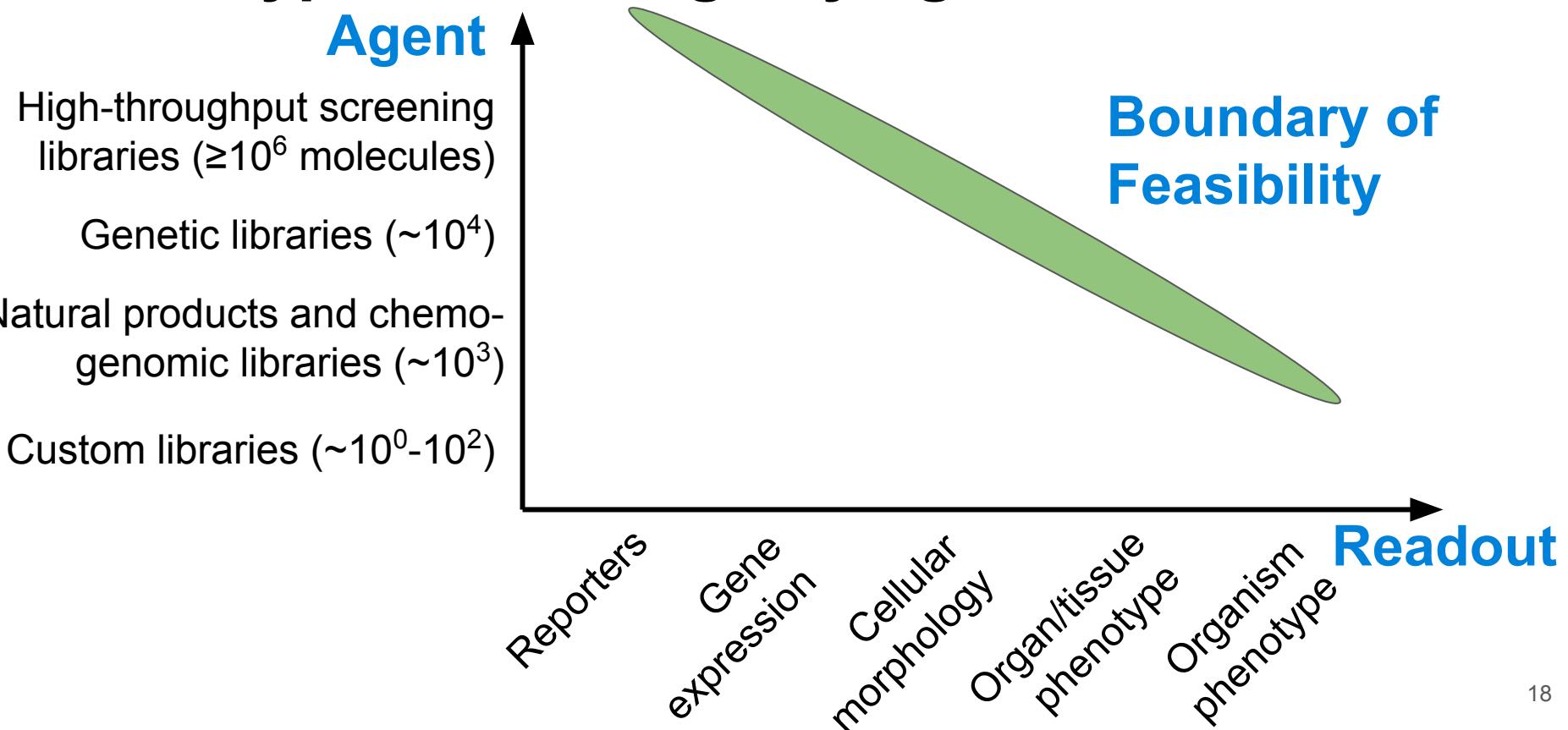


D



Roudnicky *et al.*, PNAS, 2020,
<https://www.pnas.org/content/early/2020/08/04/1911532117>

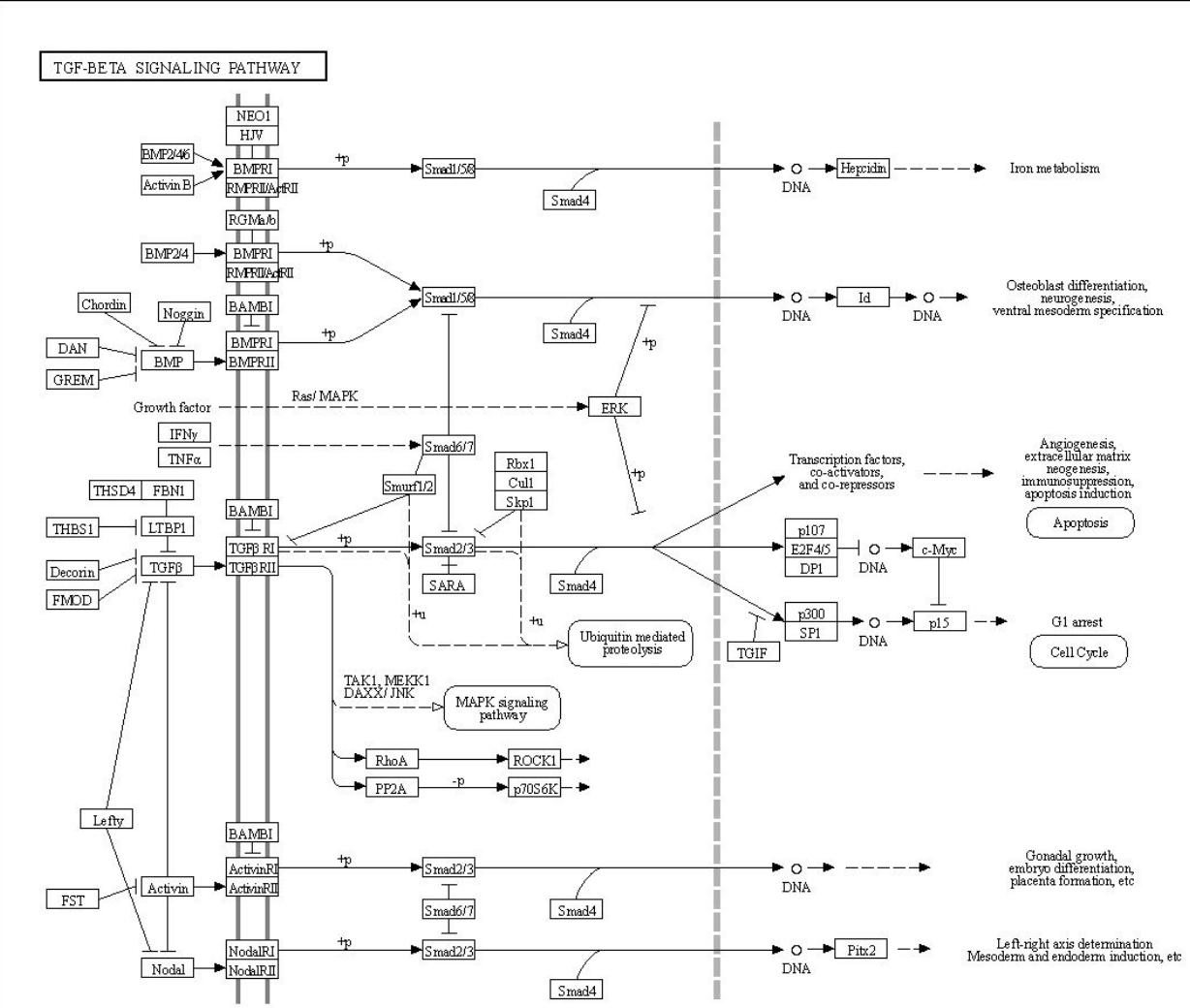
Phenotypic screenings by agent and readout



Mapping genes to biological pathways

Option 1: [KEGG pathways](#),
with the example of [TGF- \$\beta\$ signaling pathway](#).

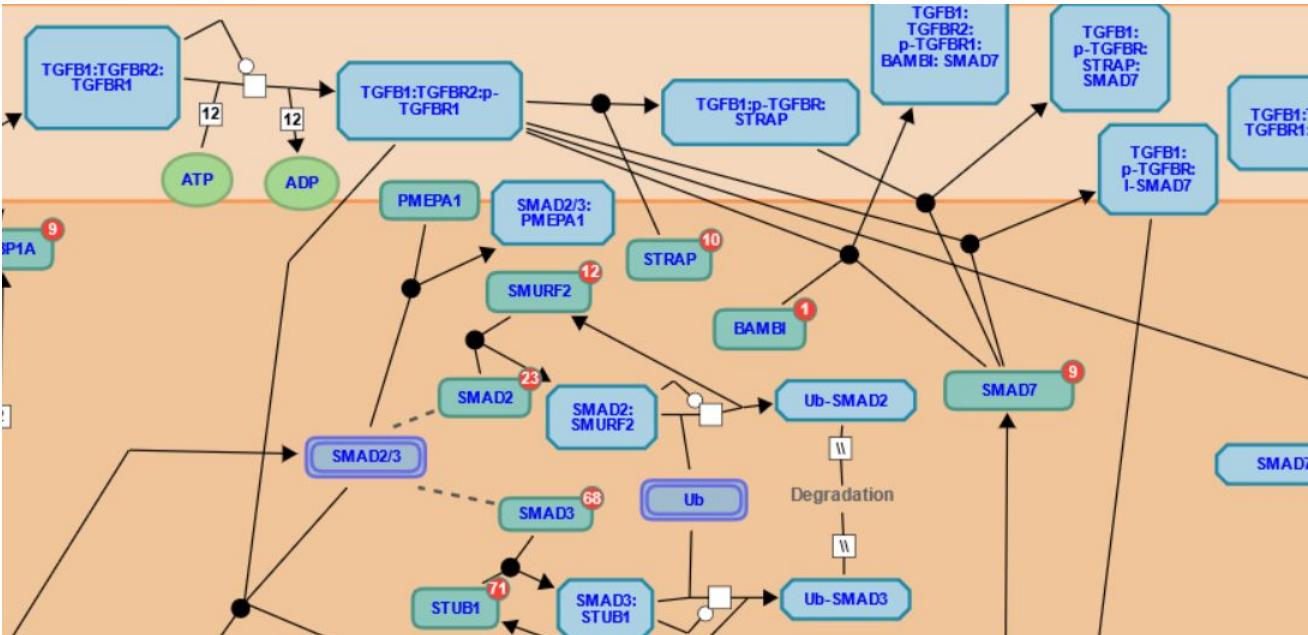
[A RESTful API](#) is available
for academic use, with
clients in Python and R.



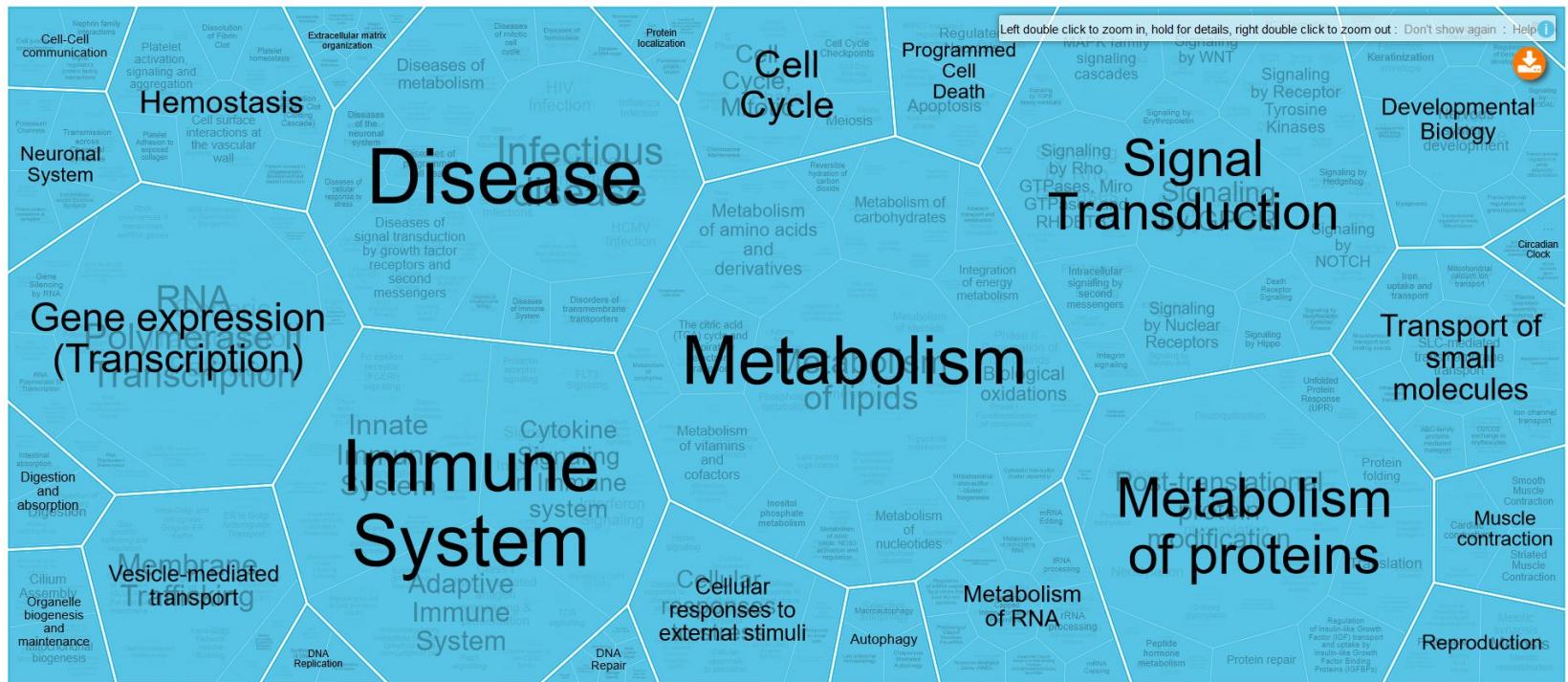
Mapping genes to biological pathways

Option 2: [Reactome](#) pathways, with the example of the [TGF- \$\beta\$ signaling pathway](#).

[Developer's Zone](#) provides API and graph database interfaces.



Overview of pathways captured by Reactome



The Voronoi (Reacfoam) view of all pathways in Reactome

Mapping genes to biological processes

- Gene Ontology
- UniProtKB keywords
- Example:

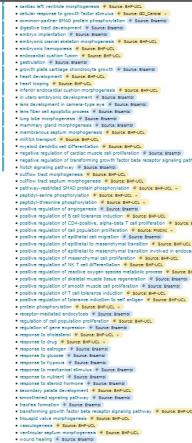
TGFBR2_HUMAN

(TGF-beta receptor type -2, P37173)



GO - Biological processⁱ

- activation of protein kinase activity  Source: BHF-UCL
- aging  Source: Ensembl
- animal organ regeneration  Source: Ensembl
- apoptotic process  Source: UniProtKB
- atrioventricular valve morphogenesis  Source: BHF-UCL
- blood vessel development  Source: BHF-UCL
- brain development  Source: BHF-UCL

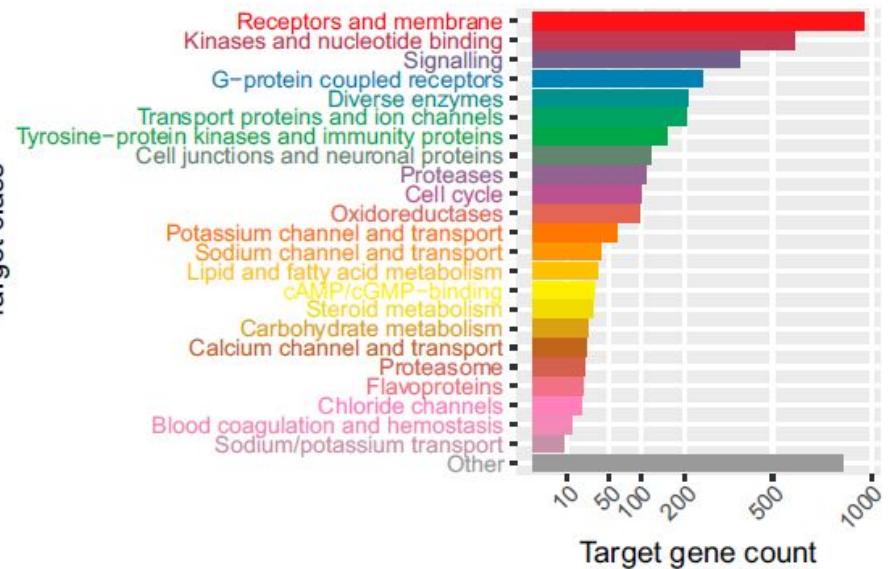


Keywordsⁱ

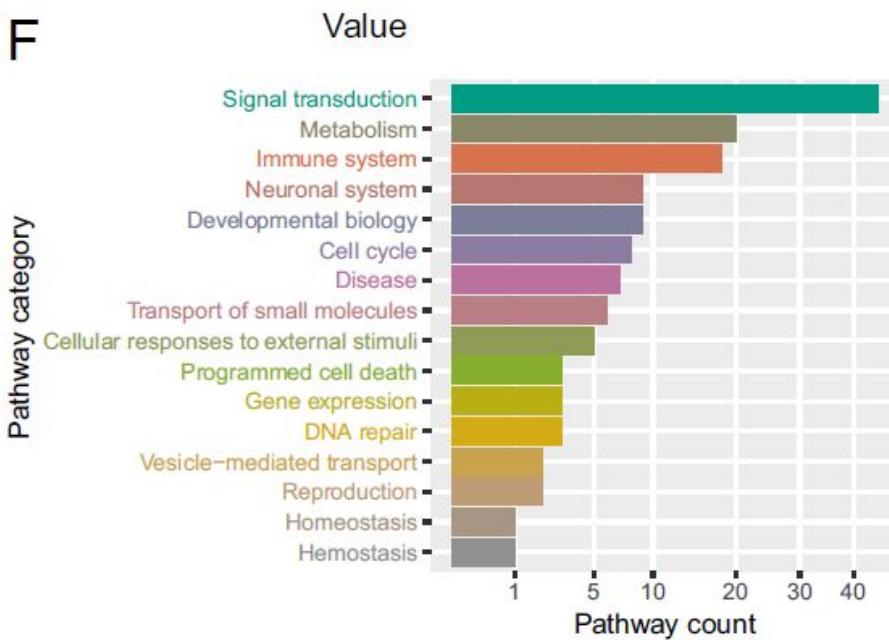
Molecular function	Kinase, Receptor, Serine/threonine-protein kinase, Transferase
Biological process	Apoptosis, Differentiation, Growth regulation
Ligand	ATP-binding, Magnesium, Manganese, Metal-binding, Nucleotide-binding

SPARK covers the target space evenly with representative, potent, and specific compounds

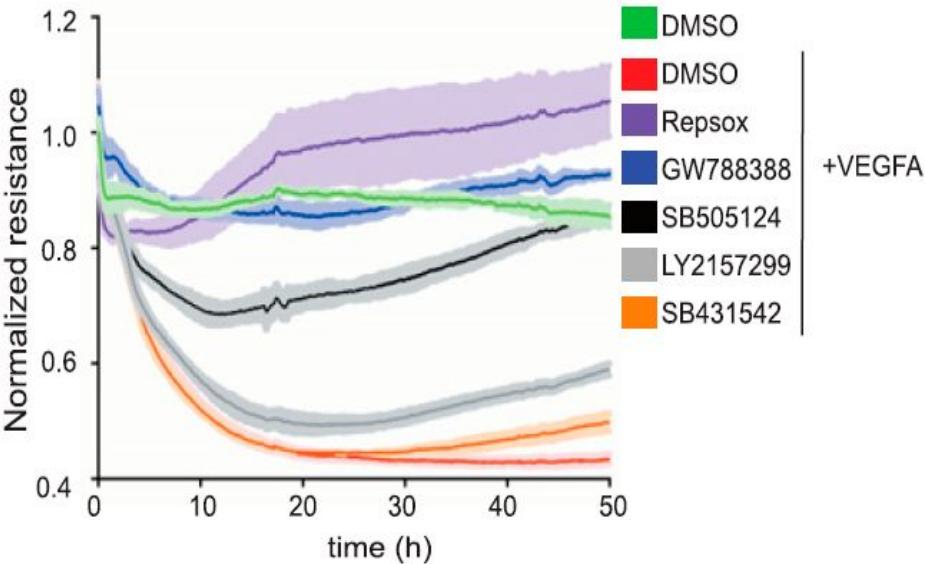
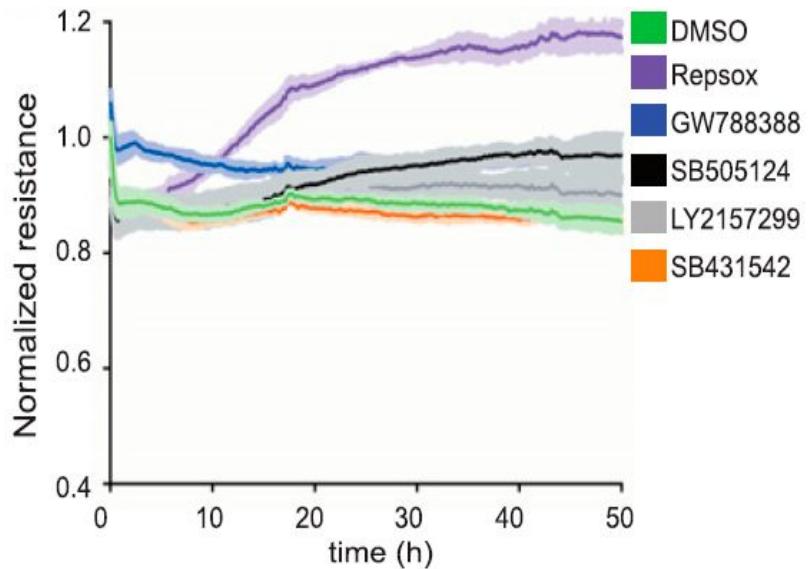
E



F

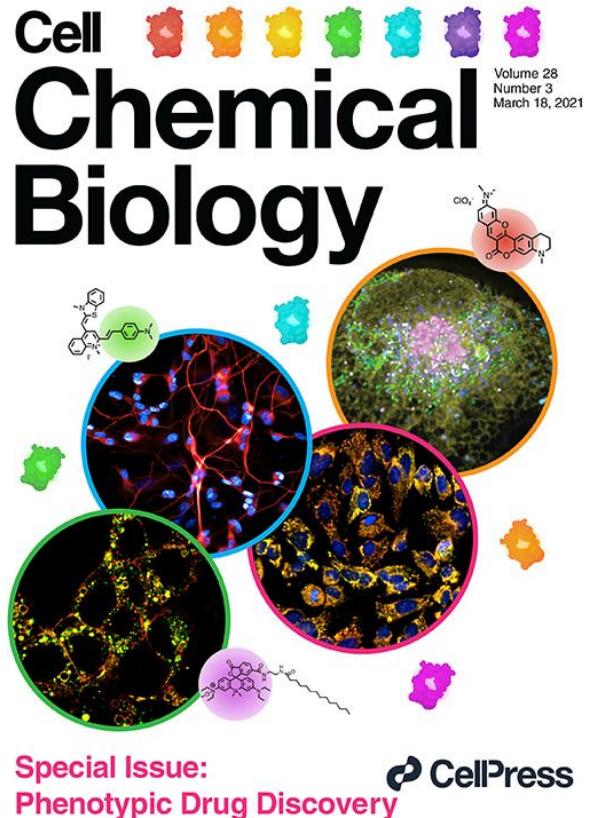


Screening with SPARK in endothelial cells identified TGF- β pathway genes as potential targets for diabetic retinopathy



Conclusions about chemogenomic library

- Phenotypic drug discovery can lead to first-in-class drugs with novel mechanisms;
- Unsupervised machine learning and data modelling contribute to build chemogenomic libraries;
- We can link drug candidates via targets to biological pathways and processes.

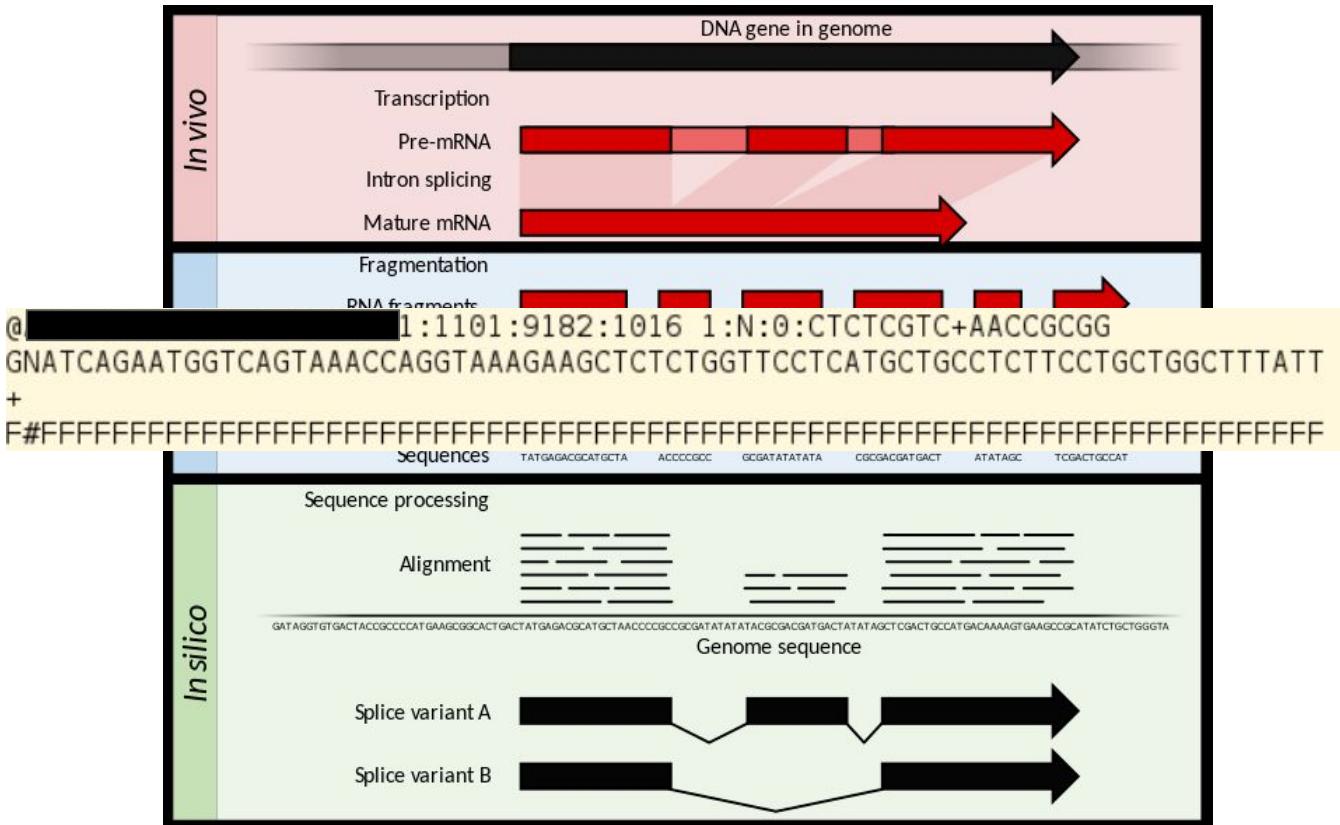


Offline activities of Module II

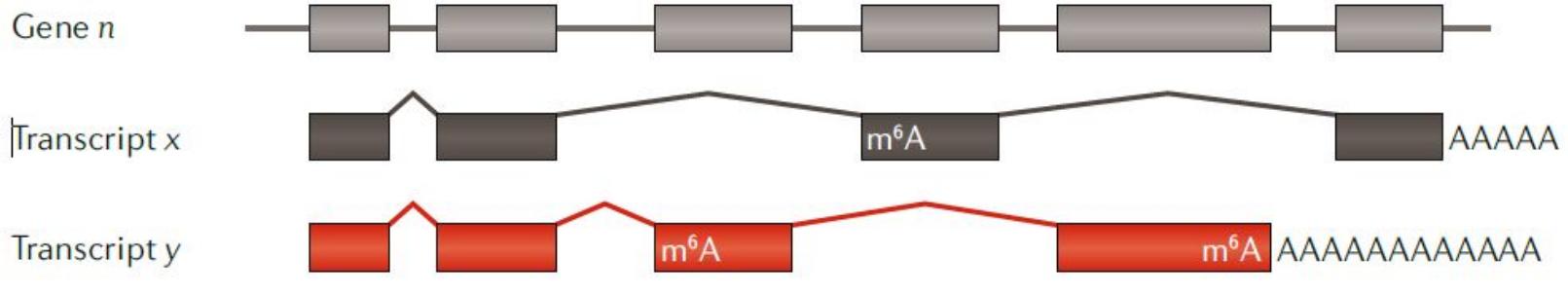
Please use your favourite programming language (shell scripts, python, R, for instance) and APIs (Application Programming Interfaces) of databases to perform following operations. Submit your code.

1. Retrieve all approved drugs from the ChEMBL database, sort them by approval year and name ([a Python example is here](#); documentations of the ChEMBL API can be found [here](#));
2. For each approved drug **since 2014** that you identified in step (1), retrieve a list of UniProt accession numbers, namely protein targets associated with the drug;
3. For each protein with a UniProt accession number that you identified in step (2), retrieve UniProt keywords associated with it. [You can use the UniProt API, documented here](#). [Python](#) and [R](#) clients are also available.

Transcriptome profiling by RNA sequencing



Transcriptome profiling by RNA sequencing



Ambiguous
to exon



Unambiguous
to exon



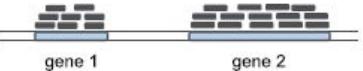
Ambiguous
to isoform



Unambiguous
to isoform



Read Mapping



Count collection

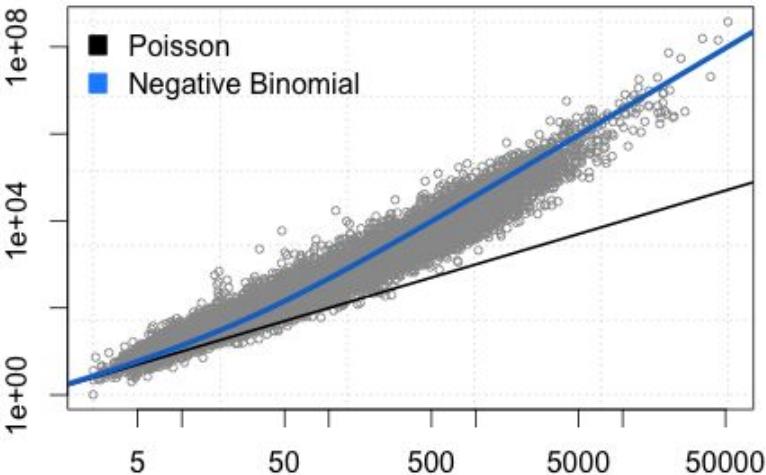
	sample A1	sample A2	sample B1	sample B2
gene 1	8	10	100	200
gene 2	14	15	15	40
gene 3	33	40	35	70
...
gene N	100	120	105	220

Normalization by library size

	sample A1	sample A2	sample B1	sample B2
gene 1	8	10	100	200
gene 2	14	15	115	40
gene 3	33	40	35	70
...
gene N	100	120	105	220

↓
Tot. reads:
5 millions Tot. reads:
10 millions

Pooled gene-level variance (log10 scale)



Tools: *edgeR* and *DESeq2*

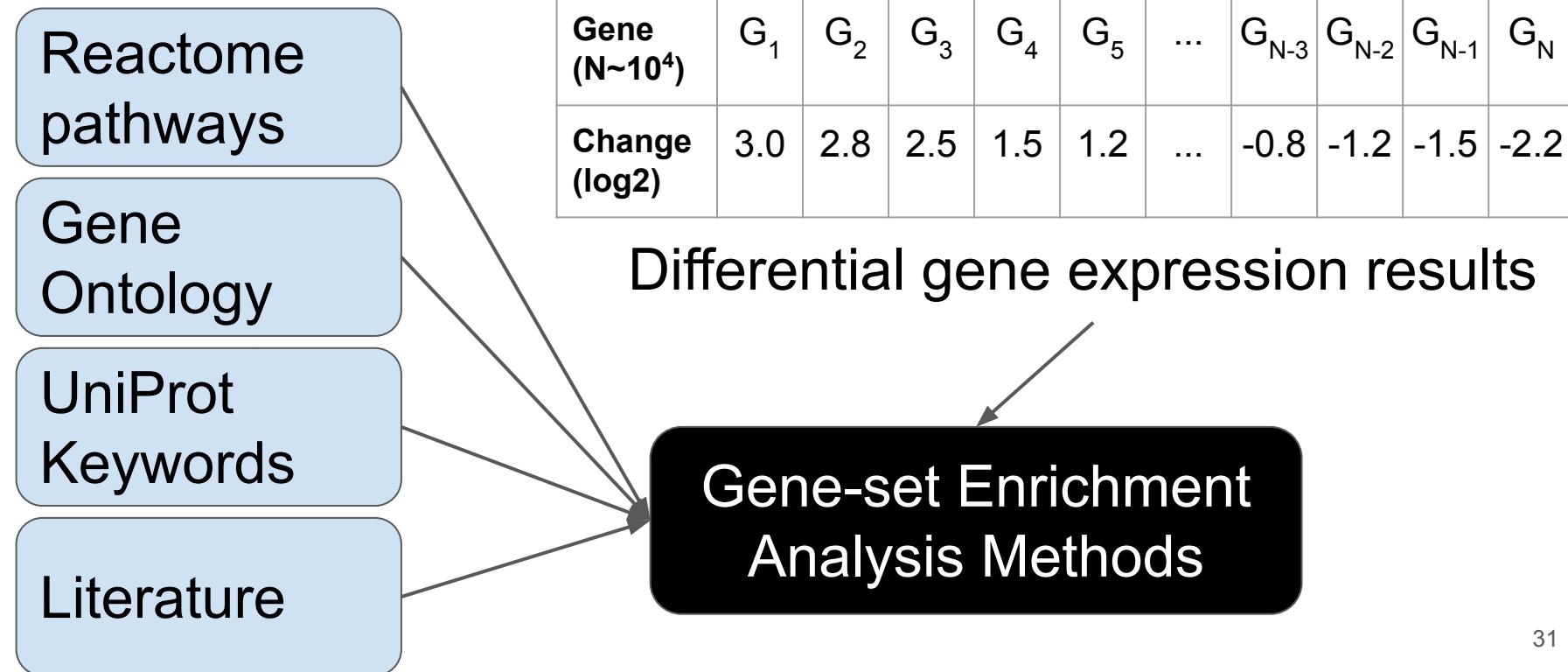
Differential Gene Expression Analysis

	sample A1	sample A2	sample B1	sample B2
gene 1	0.16	0.20	2.00	2.00
gene 2	0.28	0.30	0.30	0.40
gene 3	0.66	0.80	0.70	0.70
...
gene N	2.00	2.40	2.10	2.20

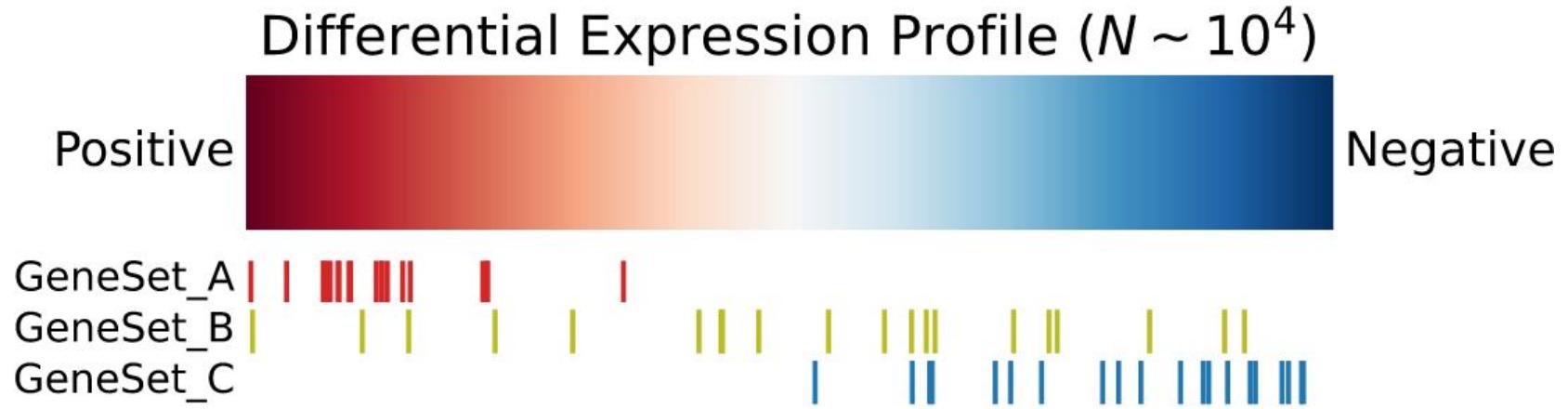
Probability theory and statistical tools discussed

- Distributions
 - Gaussian distribution (used in linear model)
 - Bernoulli distribution → Binomial distribution → Negative binomial distribution
 - Poisson distribution → Negative binomial distribution
 - Poisson distribution \longleftrightarrow Exponential distribution
- Statistical methods
 - Bootstrapping method
 - Student's t-test
 - Wilcoxon-Mann-Whitney test
 - Kolmogorov-Smirnov test

Interpret differential gene expression data with gene-set enrichment analysis



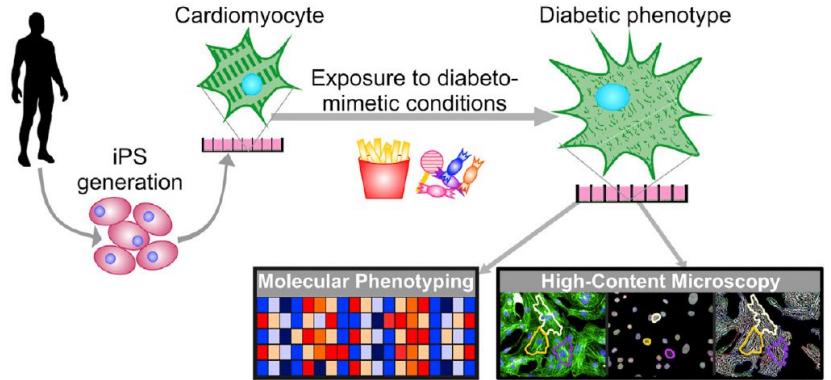
Gene-set enrichment analysis



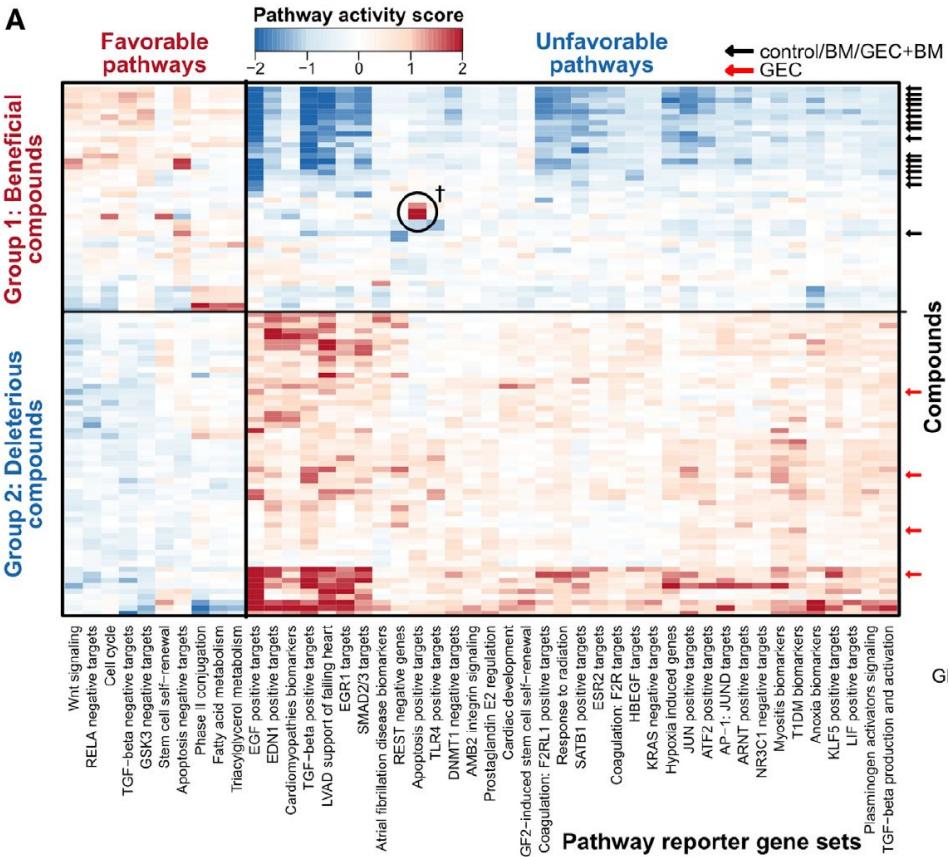
Input: (1) a differential gene expression profile; (2) a set of gene-sets $\{G\}$, each a set of genes.

Output: a ranked list of the input gene-sets by *enrichment*.

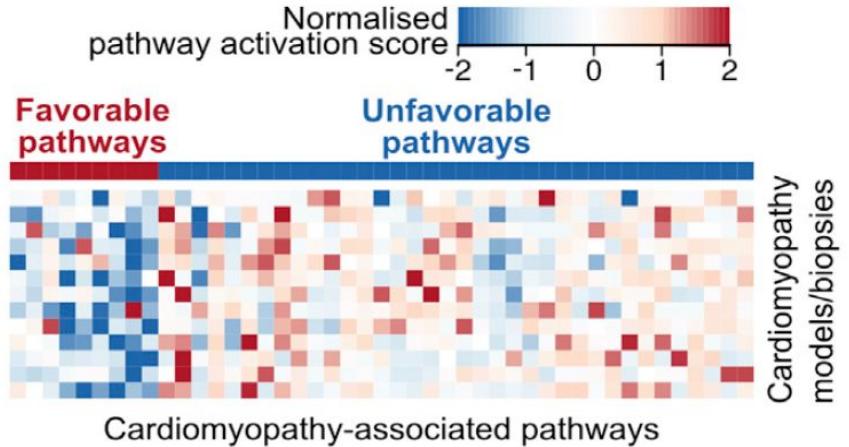
Gene expression as screening readout



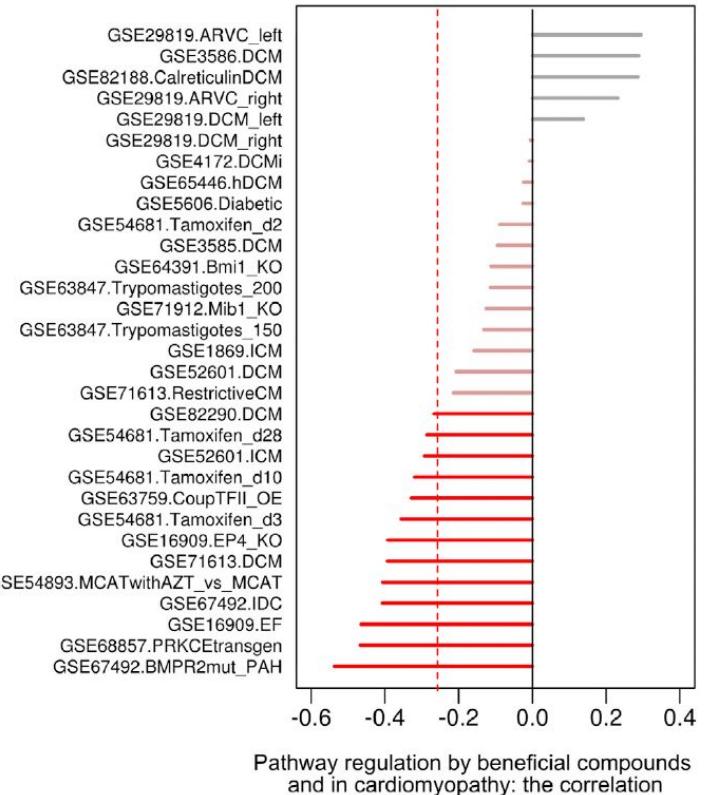
Differential gene expression profiles are molecular snapshots of drugs' action in the cell.



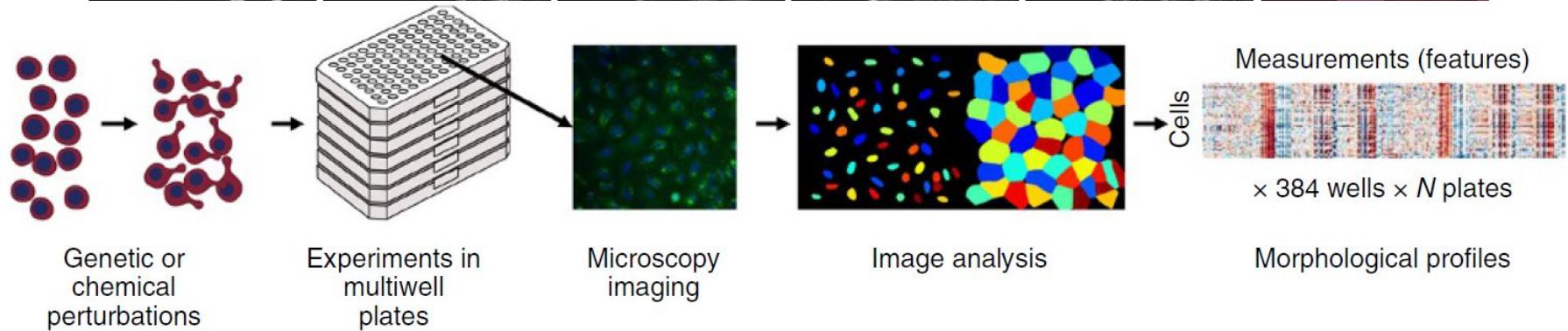
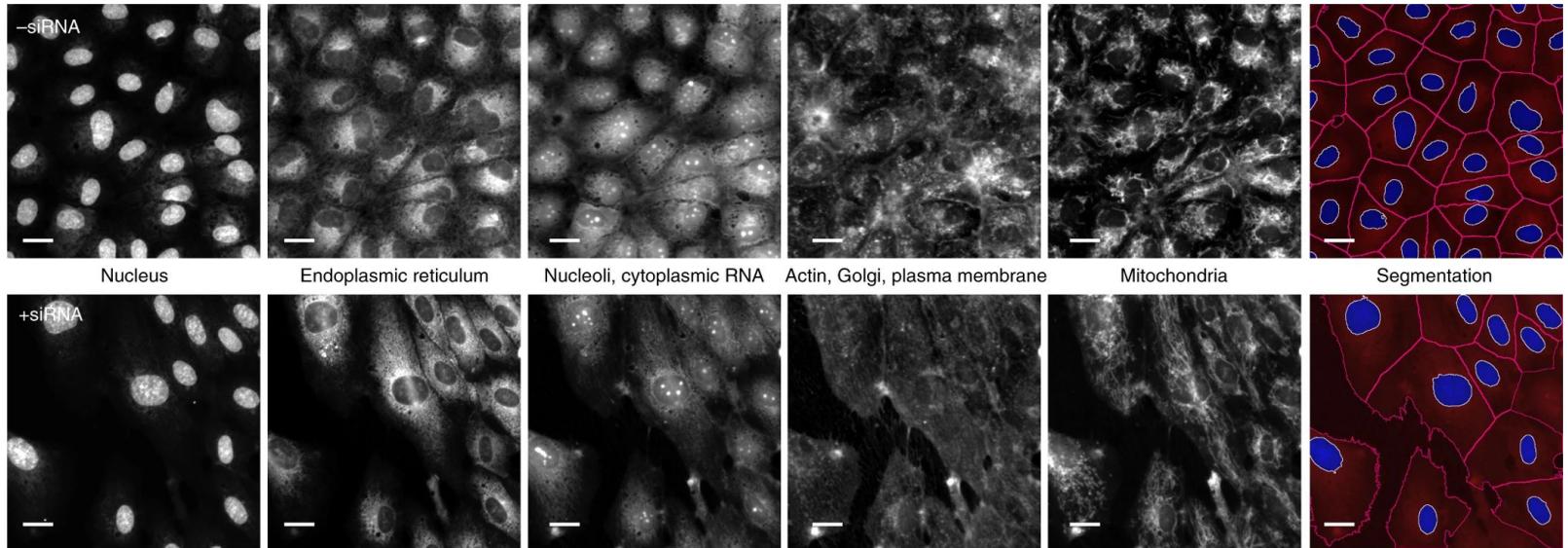
Gene expression from patient and animal models help compound selection



We can prioritise molecules that reverse disease-induced changes.

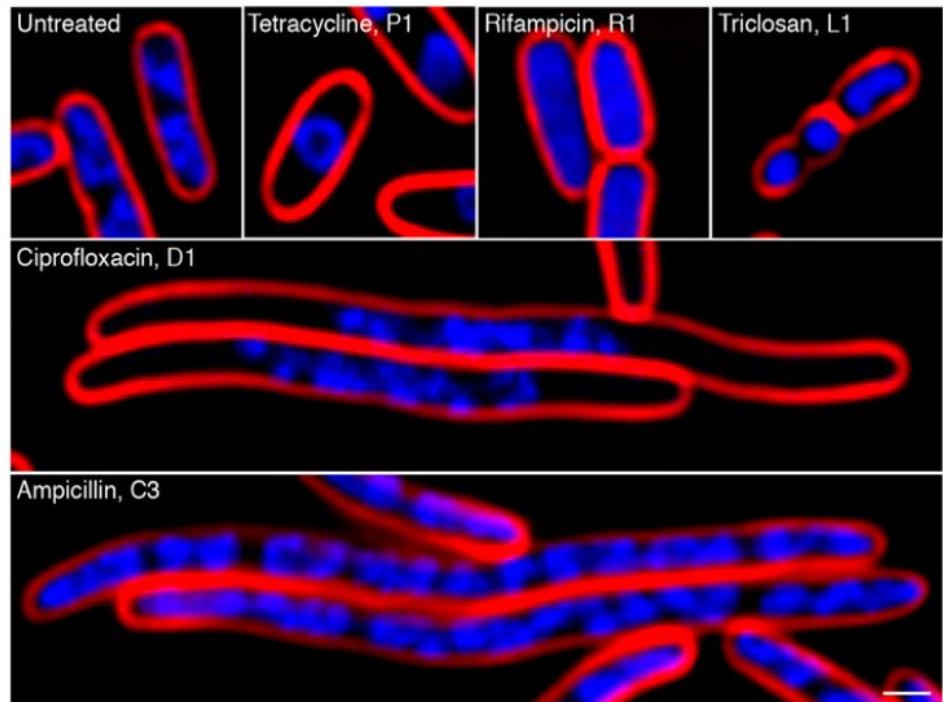


Morphology as screening readout

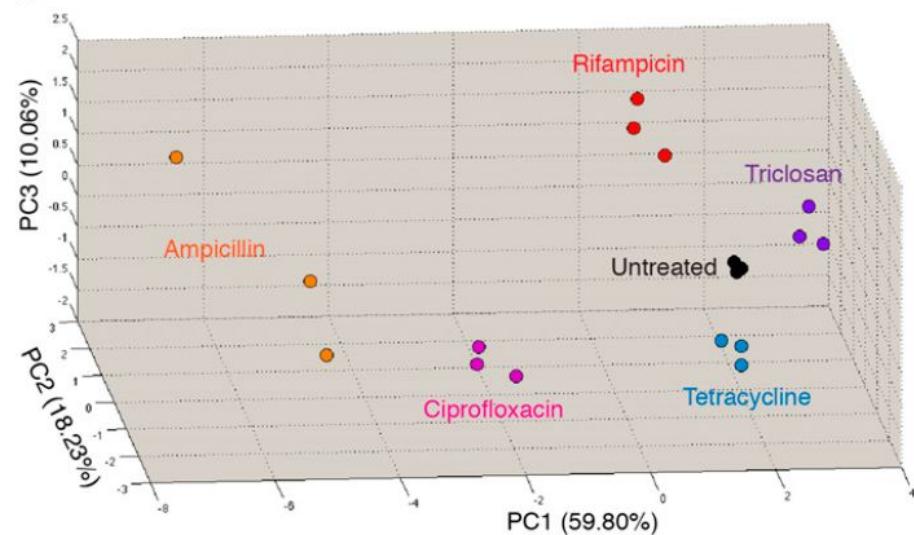


Cytological profiling for antibiotics discovery

A



B



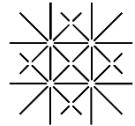
P: Protein translation inhibitors

R: RNA transcription inhibitors

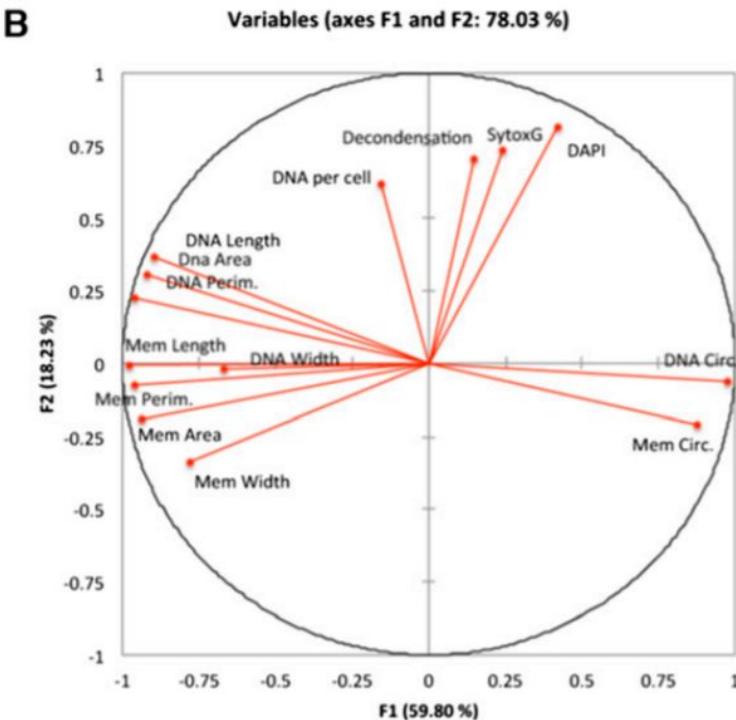
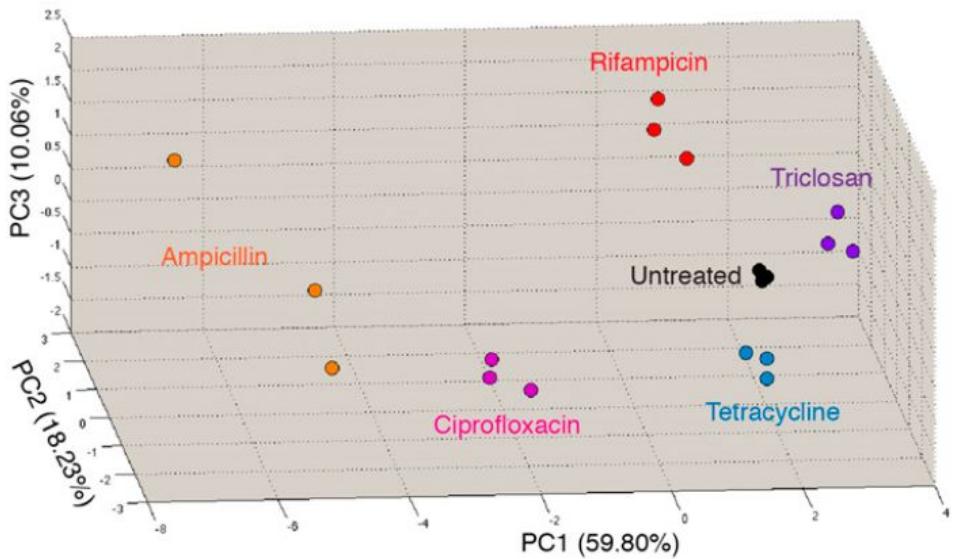
D: DNA replication inhibitors

L: Lipid biosynthesis inhibitors

C: Cell-wall synthesis inhibitors (peptidoglycan)



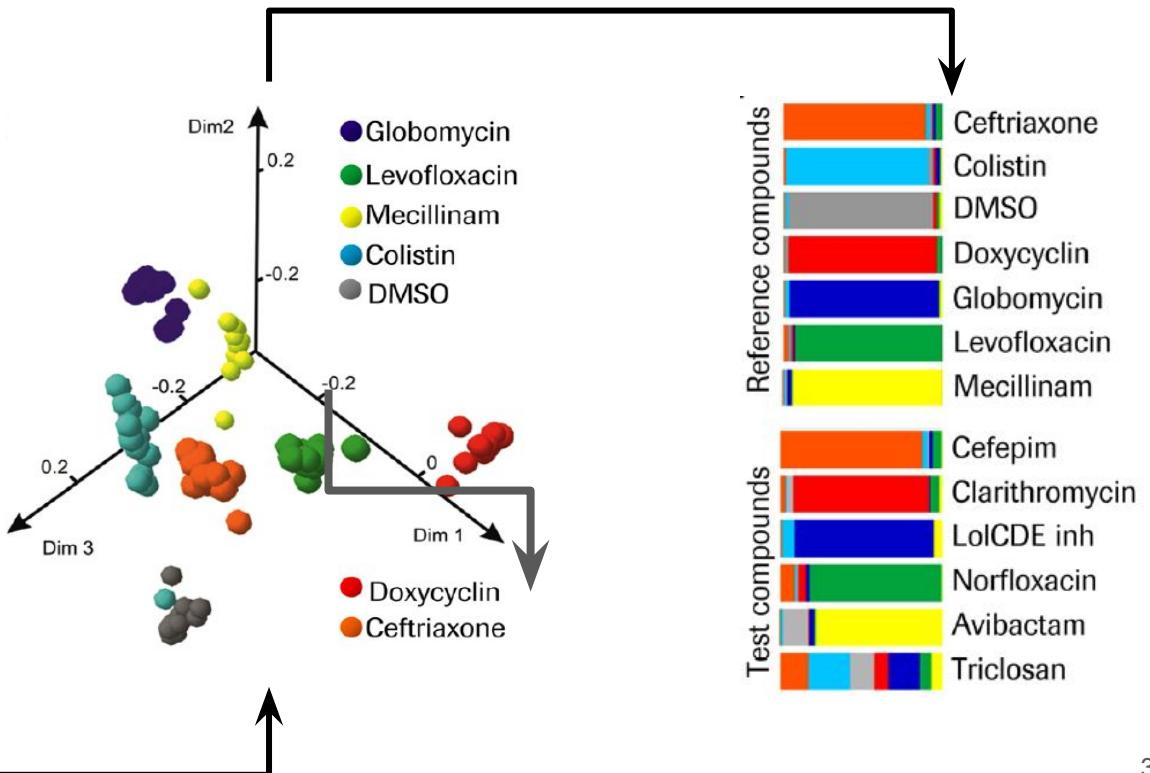
Principal components are linear combination of morphological features



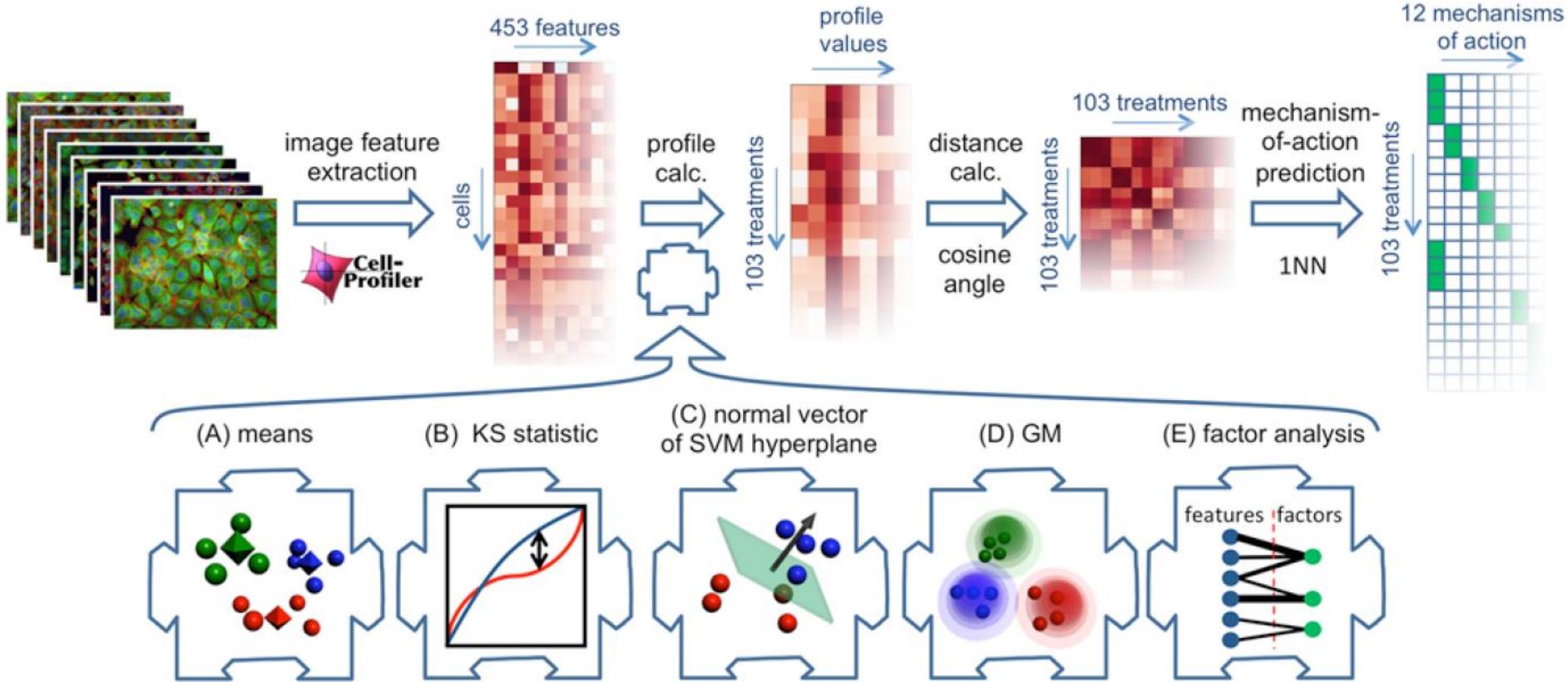
Membrane area, DNA area, Membrane perimeter, DNA perimeter, Membrane length, DNA length, No. of nucleoids per
 μm^2 μm^2 μm μm μm cell

Membrane width, DNA width,
 μm μm Membrane circularity DNA circularity SytoxG intensity DAPI intensity Decondensation

Morphology classifies compounds by MoA



Comparison of computational methods



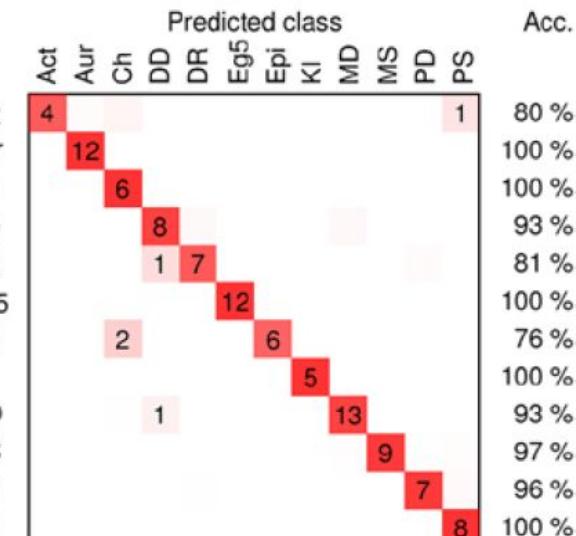
Do the benchmark and use Occam's Razor

Table I. Accuracies for classifying compound treatments into mechanisms of action.

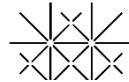
Method	Accuracy, %
Means	83
KS statistic	83
Normal vector to support-vector machine hyperplane	81
With recursive feature elimination	64
Distribution over Gaussian mixture components	83
Factor analysis + means	94

True mechanistic class

Act	Aur	Ch	DD	DR	Eg5	Epi	KI	MD	MS	PD	PS
Actin disruptors											
Aurora kinase inhibitors											
Cholesterol-lowering											
DNA damage											
DNA replication											
Eg5 inhibitors											
Epithelial											
Kinase inhibitors											
Microtubule destabilizers											
Microtubule stabilizers											
Protein degradation											
Protein synthesis											



Overall accuracy: 94 %

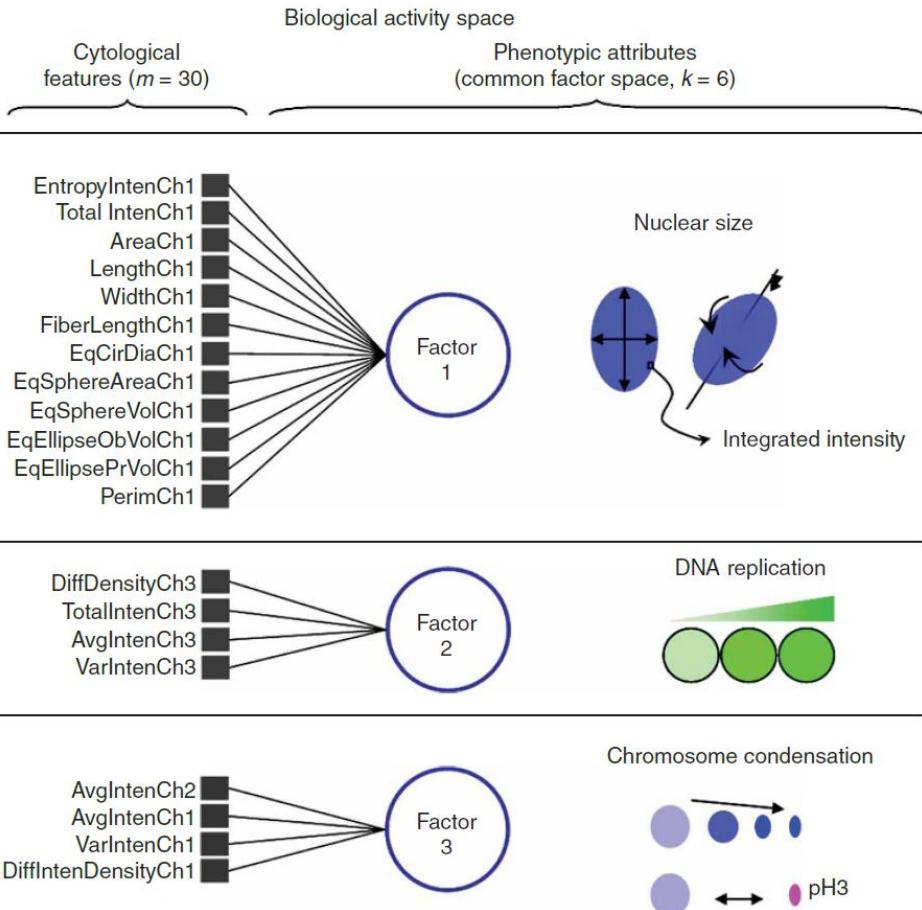


A possible explanation for the success of latent variable models

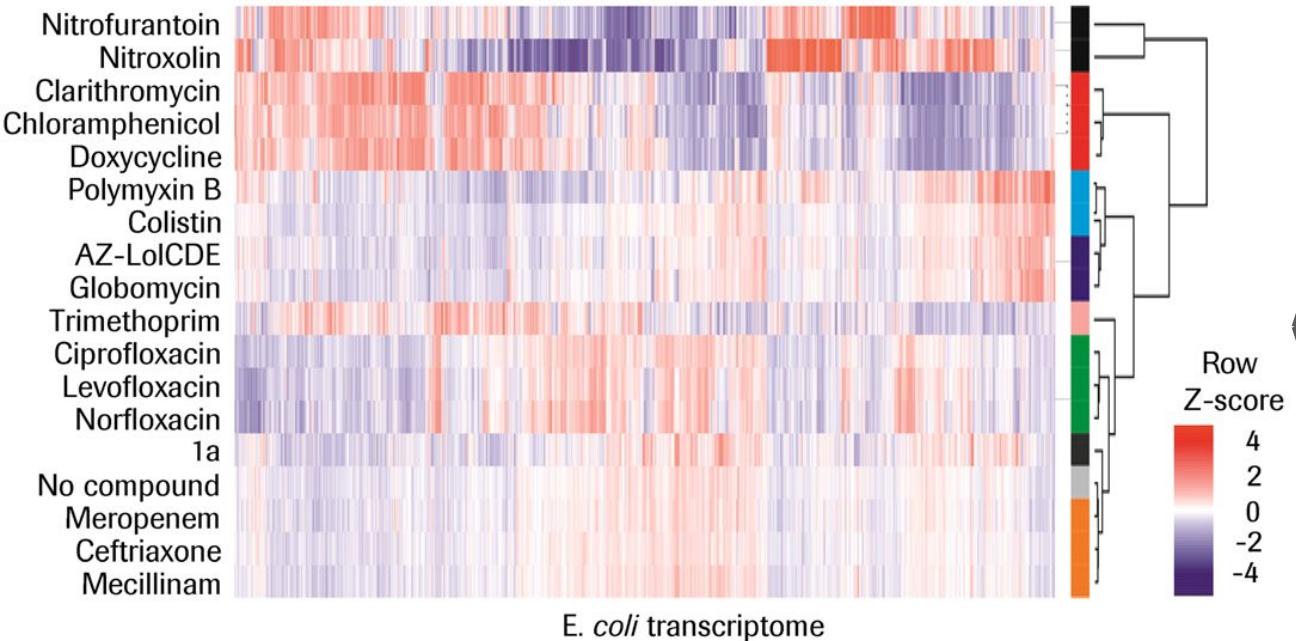
$$\text{Cells} \begin{pmatrix} x_{11} & \cdots & x_{1m} \\ \vdots & \ddots & \vdots \\ x_{nl} & \cdots & x_{nm} \end{pmatrix} = X_{nm} = \sum_{i=1}^k L_{ni} F_{im} + \varepsilon_{nm}$$

Cytological features *k*-factor space

A common latent factor model



Morphology and gene expression used jointly



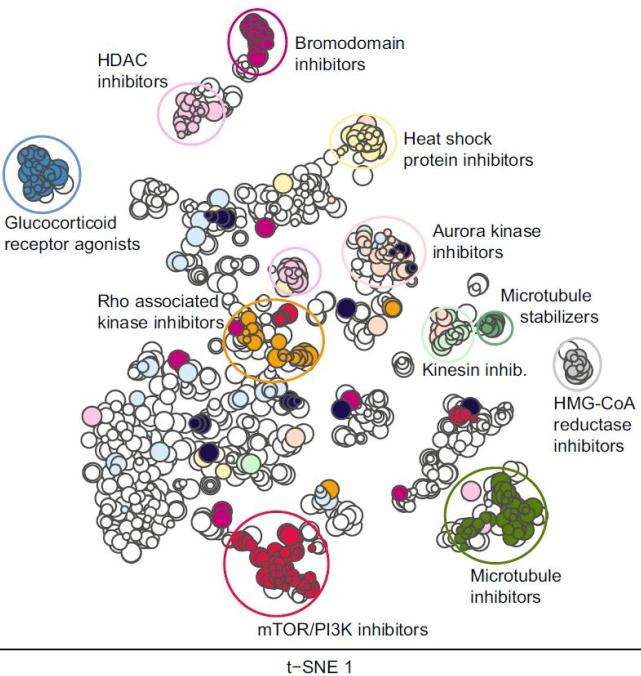
Gene-set
enrichment
analysis

Reporter
assays

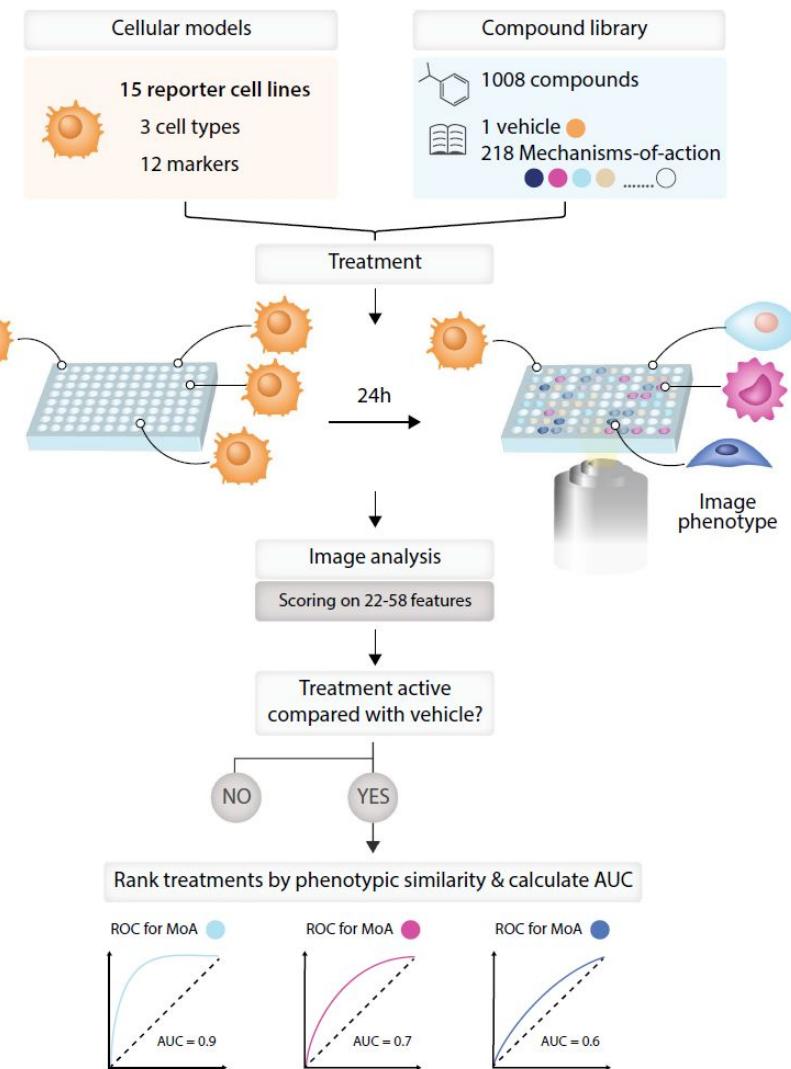
Pathway-
Phenotype
associations

A multi-cell-type, 1008-compound screening by Cox et al. (2020)

t-SNE 2



- ABL1 inhibitor
- Aurora kinase inhibitor
- Bromodomain inhibitor
- Glucocorticoid receptor agonist
- HDAC inhibitor
- Heat shock protein inhibitor
- HMG-CoA reductase inhibitor
- Kinesin inhibitor
- Microtubule inhibitor
- Microtubule stabilizer
- mTOR and/or PI3K inhibitor
- Rho associated kinase inhibitor
- VEGFR family inhibitor
- (Other)



Conclusions

- Gene expression and image-based profiling can be used individually or jointly for phenotypic screening;
- Integration of biological knowledge, high-throughput data, and statistical modelling empowers phenotypic drug discovery.

References

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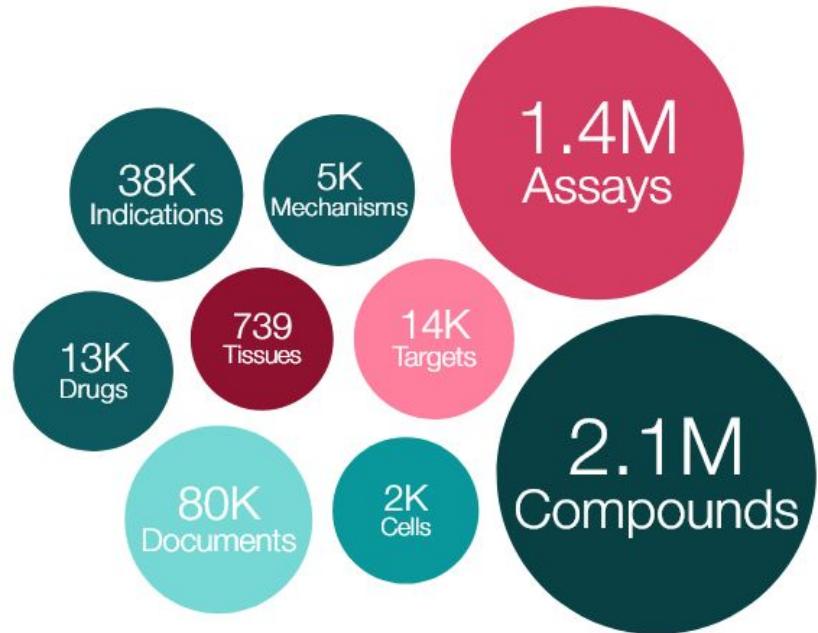
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The evolution of ChEMBL database



Visualization of ChEMBL (2021)

Visualization of ChEMBL
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